SYNTHESIS AND EVALUATION OF ANTIMICROBIAL, ANALGESIC AND ULCEROGENIC ACTIVITIES OF SOME NOVEL ISATIN SCHIFF AND MANNICH BASES SUBSTITUTED WITH CIPROFLOXACIN

Dissertation submitted to
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in partial fulfillment of the requirements for the
Degree of

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DEPARTMENT OF PHARMACEUTICAL CHEMISTRY,
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CERTIFICATE

This is to certify that the dissertation entitled **"SYNTHESIS AND EVALUATION OF ANTI MICROBIAL, ANALGESIC AND ULCEROGENIC ACTIVITIES OF SOME NOVEL ISATIN SCHIFF AND MANNICH BASES SUBSTITUTED WITH CIPROFLOXACIN"** was carried out by **Mr.S.Ramachandran**, in the Department of Pharmaceutical Chemistry, Madurai Medical College, Madurai-625 020, in partial fulfillment of the requirements for the degree of Master of Pharmacy in Pharmaceutical Chemistry under my guidance and supervision during the academic year 2009-2010.

This dissertation is forwarded to The Controller of Examinations, The Tamil Nadu Dr.M.G.R Medical University, Chennai.

Station: Madurai (**Mrs. R.THARABAI)**

Date :

GENERAL INTRODUCTION

Drug discovery has its beginning the root of mankind [1].

Medicinal Chemistry is an interdisciplinary science that by its very nature encompasses the sciences of chemistry, biochemistry, physiology, pharmacology and molecular modeling. It has been stated that medicinal chemistry concern the discovery, the development, the identification and interpretation of the mode of action of biologically active compounds at molecular level [2].

Medicinal chemistry involves the identification, synthesis, and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties and their quantitative structure activity relationships (QSAR).

Early drug design started with elucidation of the structure of the natural products, followed by selective changes in the molecule. To improve therapeutic properties is to identify that portion of a natural molecule responsible for its biological activity and synthesis new molecules that are based on it.

The synthetic compounds Offered an Opportunities to medicinal screening. The inventions of new lead molecules are used to design effective and safe drugs and also to reduce drug toxicities [3].

So, Medicinal Chemistry plays a vital role in identification of lead compounds and through molecular modification new compounds could be synthesized and thereby it helps in the eradication of fatal disease in human being[1].

OUTLOOK OF ISATIN

Isatin is a resourceful endogenous heterocyclic molecule identified in human being and rat tissues[4]. Isatin, chemically known as 1H-Indole-2, 3-dione, has become a popular topic due to its various uses.

Isatin was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric acid and chromic acids. The synthetic Versatility of isatin has led to the extensive use of this compound in Organic Synthesis[5].

The chemistry of Isatin and its derivatives is particularly interesting because of their potential application in medicinal chemistry. Compounds of the isatin series are multifunctional compounds from which it is possible to synthesis an enormous number of assorted organic compounds.

The presence of several reaction centers in isatin and its derivatives makes it possible to bring these compounds into various types of reactions. Thus, keto group at position 2 and particularly, at position 3 can enter into addition at the c-o bond and into condensation with release of water.

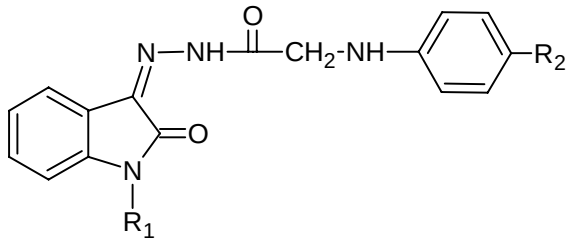
Through the NH group compounds of the isatin series are capable of entering into N-alkylation and N-acylation and into the Mannich and Michael reactions[6]. The synthetic versatility of Isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives.

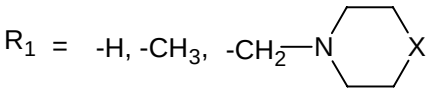
Schiff and Mannich bases of Isatin derivatives are reported to show variety of biological activities like antibacterial, antifungal, anticonvulsant, anti HIV, anti depressant and anti inflammatory activities[7].

All the synthesized isatin derivatives were evaluated for their antimicrobial, analgesic and ulcerogenic activities.

LITERATURE REVIEW

1. **Rajendra et.al.,** synthesized 3-Aryl glycyl hydrazono -2-indolinone derivatives as amoebicidal and antibacterial agents.[8]

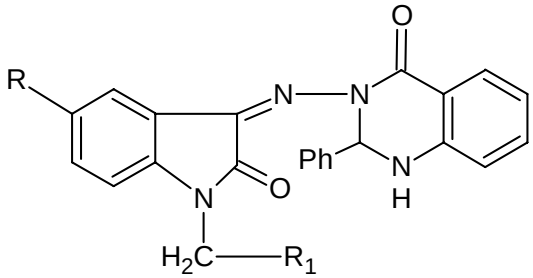




Where X = O, CH_2

R_2 = -H, -Cl, -Br, $-CH_3$, $-OCH_3$

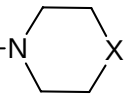
2 **M. Sarangapani et.al.,** synthesized 1-(N,N – disubstituted amino) methyl -3-imino – (2- phenyl -3,4 –dihydro -4-oxo-quinazolin-3-yl) indol-2-one.[9]



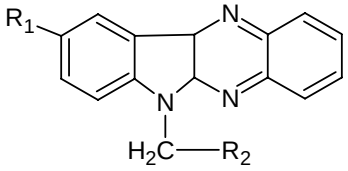
Ph= Phenyl

R = -H, $-CH_3$, -Br

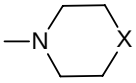
Where X = O, CH_2

R_1 = $-N(CH_2OH)_2$, $-N(C_6H_{11})_2$, 

3 **S.K. Sridhar et.al.,** synthesized N- Mannich bases of 10- H- indolo (3,2, -b) Quinoxalines. [10]

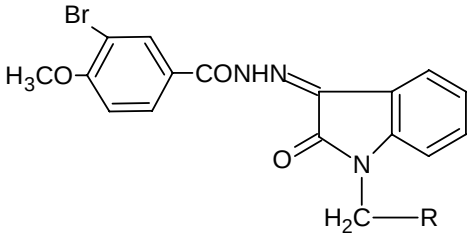


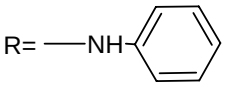
R_1= -H, -Cl, $-CH_3$

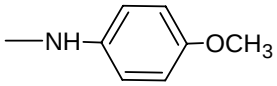
R_2= $-N(CH_3)_2$, $-N(C_2H_5)_2$, 

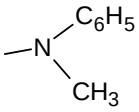
where X= O,CH_2

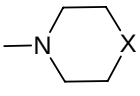
4. **Freddy H. Havaldar et.al**., synthesized 1-(substituted amino methyl)-3-(3'-bromo-4'methoxy Benzoyl hydrazono) indolin-2- one .[11]



R= 

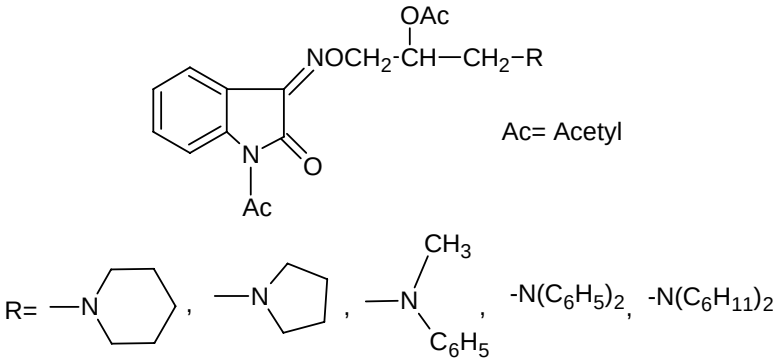
, 

, 

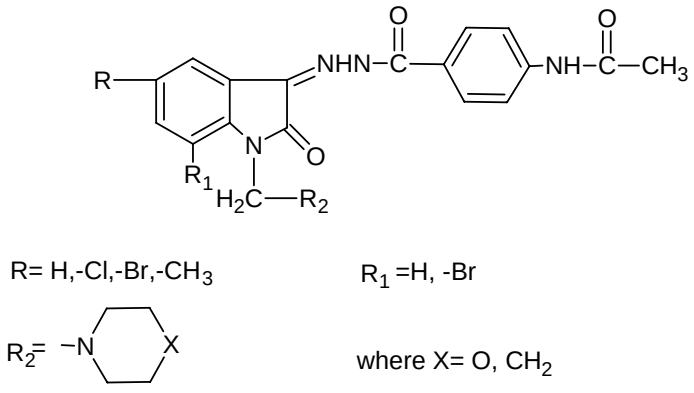


where X=O,CH_2

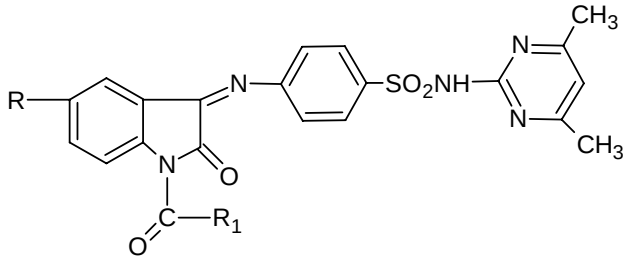
5. **A.K. Pathy et.al.,** synthesized 1-acetyl-3-(2-acetoxyl-3-substituted propyl)oximino indol- 2-(3H)one.[12]



6. **R.S. Varma et al.,** synthesized 1-Heterocyclic amino methyl 3-(4'-acetyl amino-3'-Chlorobenzoyl hydrazono)-2-indolinone as potential antimycotics.[13]



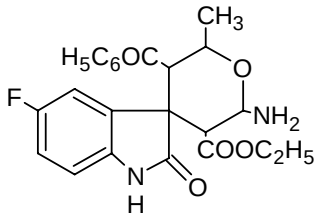
7. **P.Selvam et.al.,** Synthesized 4-(1-3-disubstituted 2-oxo-1,2 dihydro-indol-3-ylideneamino) N-[4,6 Dimethyl –pyrimidin-2-yl]-benzene sulphonamides were reported to possess antiviral activity.[14]



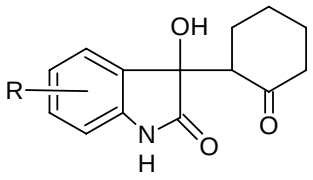
R = H, Cl

R_1=CH_3, C_6H_5

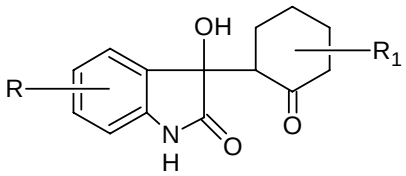
8. **Jain and Bansal** synthesized heterocyclic derivatives of isatin and studied anticonvulsant activity in rats.[15]



9. **Pajovhesh et al.,** synthesized a series of cyclohexane and other cyclic ketone derivatives of isatin and Screened them for anticonvulsant activity.[16]



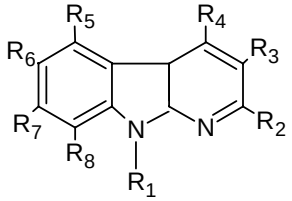
R= H, 1-$CH_2C_6H_5$, 5-Br, 5-Cl, 5-CH_3, 5-OCH_3, 5-NO_2, 6-Cl, 7-CH_3,
4-Cl-7-CH_3, 4-Cl-7-OCH_3, 5-Cl-7-CH_3, 6-Cl-5-OCH_3, 6-Cl-7-CH_3



R= H, 1-CH3, 5-Br, 5-NO2, 4-Cl-7-CH3

R1= 2-methyl cyclohexanone, 2-cyclohexyl cyclohexone,
3- methyl cyclohexanone

10. **Olesen and Kanstrup** prepared pyrido[2,3-b] indoles to treat epilepsy, senile dementia and Parkinsonism.[17]



R_1 = H, C_{1-6} alkyl (CH_3, C_2H_5, C_3H_7-C_6H_{13})

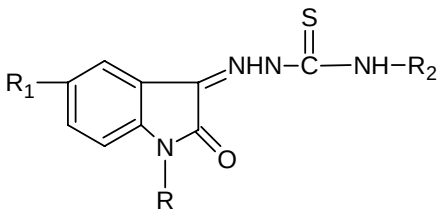
R_2 = piperidino, morpholino

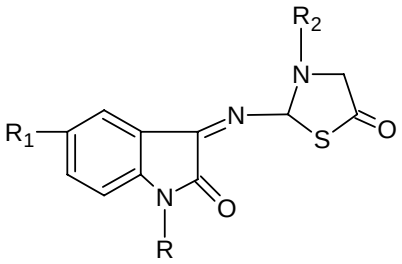
R_3 =H, COOH, CN

R_4= H, C_{1-6} alkyl (CH_3, C_2H_5, C_3H_7)

R_5-R_8 = H, NO_2, NH_2

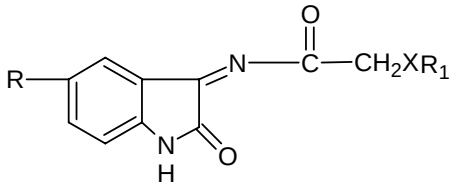
11. **Karali et.al .,** synthesized a series of 3-thiosemicarbazono-2-indolinones and studied anticonvulsant Activity. [18]





R= H, $COCH_3$ R_1 = H, Br R_2 = CH_3, C_2H_5, C_6H_5

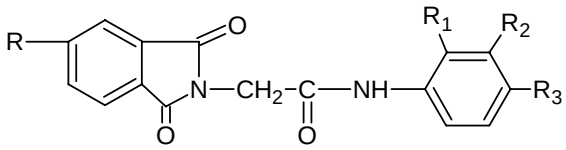
12**. Gursoy and Karali** synthesized a series of 3-aryloxyl, arylthioxy acetyl hydrazono-2-indolinones and studied anticonvulsant activity.[19]



X= O, S R= H,Br

R_1= C_6H_5, 3-CH_3-C_6H_4 4, 5 diphenyl –(1-H)- imidazol-2-yl

13. **Ghaney and EI- Helbyl** synthesized 1,3 dioxo –n-phenyl -2H iso indol-2-acetamide and studied anticonvulsant activity.[20]

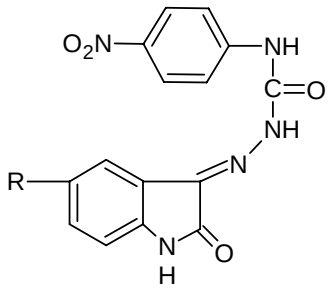


R_1= H, CH_3, Halogens, OH

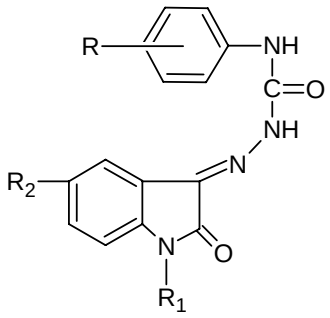
R_2= H, CH_3, Br

R_3= H, CH_3, Br, Cl

14. **S.N Pandeya et al**., synthesized p- nitrophenyl substituted semicarbazone and their anticonvulsant activity was screened against Maximal Electric Shock test.[21]



R= H, Cl, NO_2

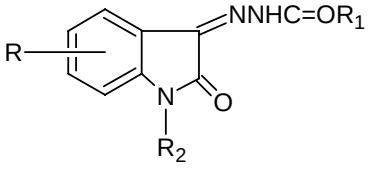


R = 2-Cl, 3-Cl, 4-Br, 4-NO_2, 4- SO_2NH_2

R_1= CH_3, $COCH_3$

R_2= H, NO_2

15. **S.N Pandeya et al**., synthesized halo substituted isatin semicarbazones and screened for anticonvulsant activity.[22]

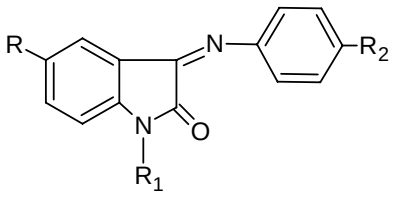


R = H, 4-Cl, 5-Cl, 6-Cl

R_1= CH_2O-C_6H_5, 1-(CH_2O)-(4-Br)-C_6H_4

R_2= $COCH_3$, $CH_2C_6H_5$

16. **S.N Pandeya et al**., synthesized various Schiff bases of isatin derivatives and screened them for anticonvulsant activity.[23]

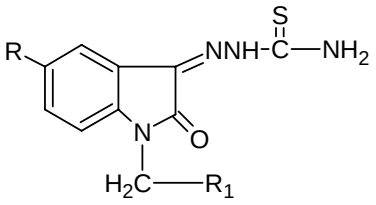


R = Br, NO_2

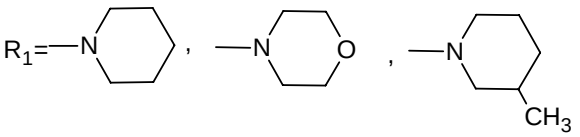
R_1= CH_3, $COCH_3$

R_2=NO_2, COOH, OCH_3, Cl, F

17. **Varma and Nobles** investigated various Isatin –N-Mannich bases of isatin-3 thiosemicarbazone derivatives against viral, fungal and antibacterial organisms.[24]

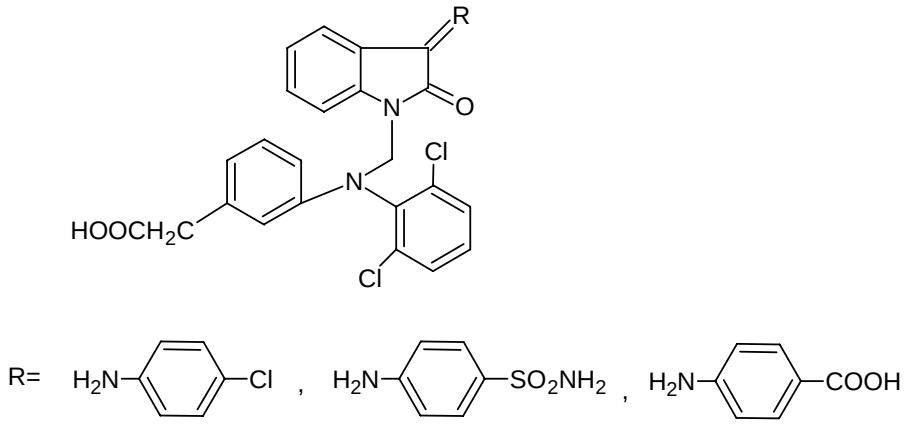


R= H, CH_3, Br

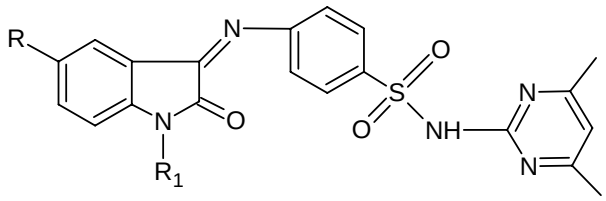
R_1= 

$-N(C_2H_5)_2$

18. **V.Ravichandran et.al**, synthesized mannich bases of isatin and its derivatives with 2-[(2, 6 dichloro phenyl)amino] phenyl acetic acid.[25]



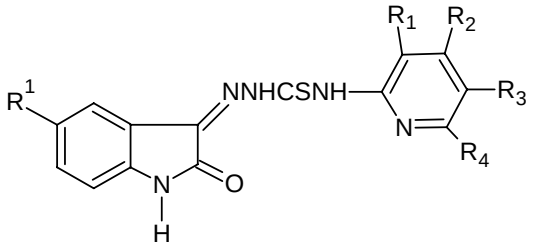
19. **Periyasamy Selvam et.al,** synthesized 4-[(1, 2-dihydro-2-oxo-3H-indol-3-ylidene) amino] N-(4, 6-dimethyl-2-pyridin-2-yl)benzene sulphonamide and its derivatives as antiviral agents.[26]



R= Br, Cl, F, H, CH_3

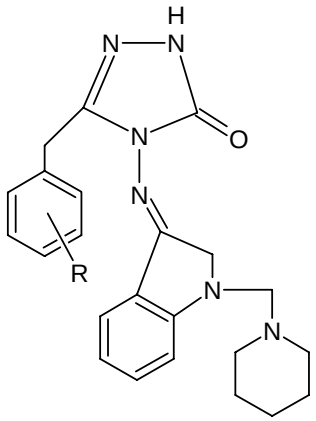
R_1= H, $COCH_3$

20. **Vijay Anandhi M., et.al.,** synthesized 1-(5-substituted-2-oxo indolin-3-ylidine)-4 (substituted Pyridine-2yl) thiosemicarbazide as antimicrobial agents.[27]



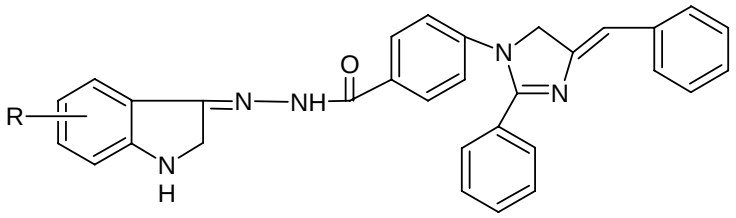
R^1 = F, Cl, Br, R_1 = H, CH_3, R_2 = H, CH_3, R_3 = H, Cl R_4 = H,CH_3

21. **Okay Bekirkan et.al.,** synthesized Schiff and Mannich bases of Isatin derivatives with 4 amino-4,5 dihydro-1,4-1,2,4-triazole-5-ones.[28]



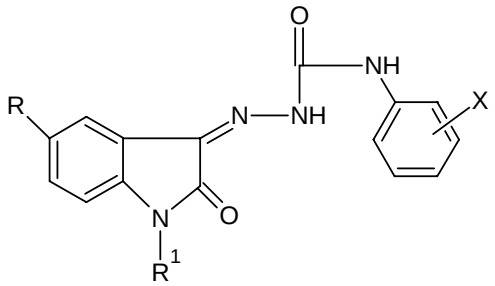
R = 2-F, 4-F X = H, Cl

22. **Ankur Patel et.al,** synthesized some new Isatin derivatives as antimicrobial agents.[29]



R = H, 5-Cl, 5-F, 5-Br, 4-Cl, 5-CH_3,

23. **Sivakumar Smitha et.al,** synthesized N-acetyl methyl isatin derivatives as anticonvulsant and Sedative-hypnotic agents.[30]

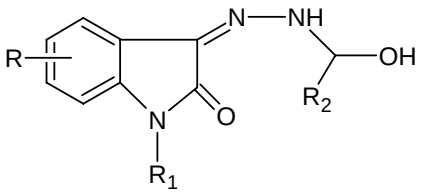


R = H, 5-Br, 5-NO_2

X = 4-Cl, 4-NO_2, 2-Cl, 4-SO_2NH_2

R1 = $COCH_3$, CH_3

24. **Surendranath Pandeya et.al,** synthesisized Isatin semicarbazones as novel Anticonvulsants.[31]

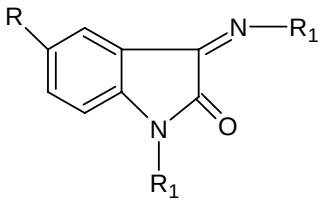


R = 4-Cl, 5-Cl, 6-Cl, H

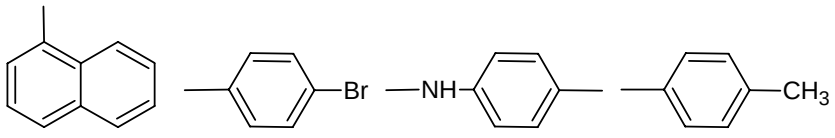
R1 = H, $COCH_3$, COC_6H_5

R_2 = 2-Chloro phenyl amino, 4-Nitro phenyl amino, 4-Bromo phenyl amino

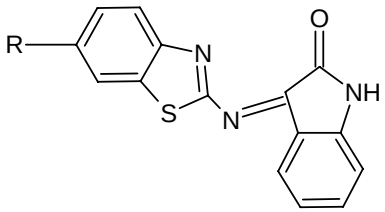
25. **Seshaiah Krishnan Sridhar et.al.,** synthesized Hydrazones, Schiff and Mannich bases of Isatin derivatives.[32]



R = H, Cl, Br , R2 = H, $-CH_2-N(C_6H_5)_2$

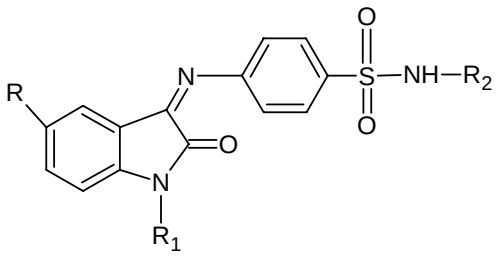
R_1 = 

26. **Prince .P. Sharma et al.,** synthesized some Novel Isatin Schiff's bases as anticonvulsant agents.[33]



R = H, $N(CH_3)_2$, Cl, OCH_3, Br, CH_3, C_2H_5, OC_2H_5, OC_2H_5, NO_2, F

27. **P.Selvam et al.,** synthesized Novel Isatin Sulphonamides as antiHIV agents.[34]



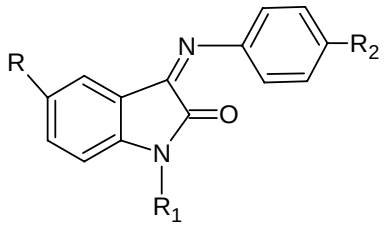
R = H, CH_3, Cl, Br

R_1 = H, CH_3, COCH

R_2 = H, 4,5 Dimethyl-2-isoxazolyl,

4,6 dimethyl-2-pyrimidinyl

28. **Manjusha Verma et.al.,** synthesized Schiff bases Isatin derivatives as anticonvulsant agents.[35]

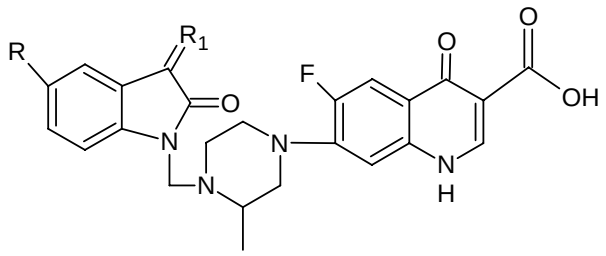


R = Br, NO_2

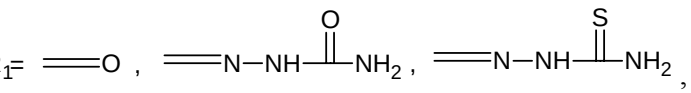
R_1 = CH_3, $COCH_3$

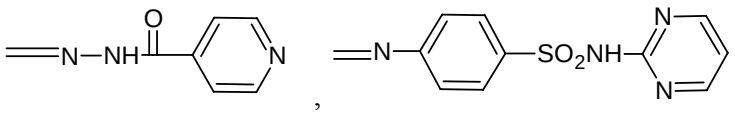
R_2 = NO_2, COOH, OCH_3, Cl, F.

29. **Dharmarajan Sriram et.al.,** synthesized Gatifloxacin derivatives as antimycobacterial agents.[36]

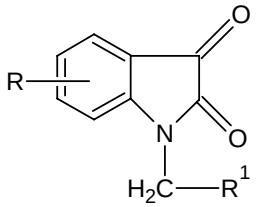


R = H, F, Cl, CH3.

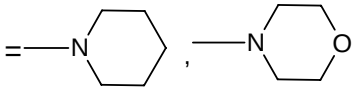
R_1= 



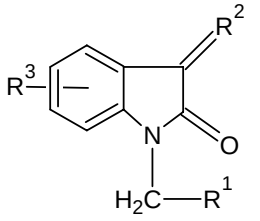
30. **Varma et.al.,** synthesized isatin –N- mannich bases and screened for antimicrobial activity.[37]



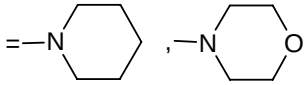
R = H, Br, R^1= - $N(C_2H_5)$



31**. Kupinic etal.,** synthesized a congenial series of isatin –N- Mannich bases and evaluated their antimicrobial activity.[38]



R^1=$N(C_2H_4OH)_2$, $N(C_2H_4Cl)_2$,

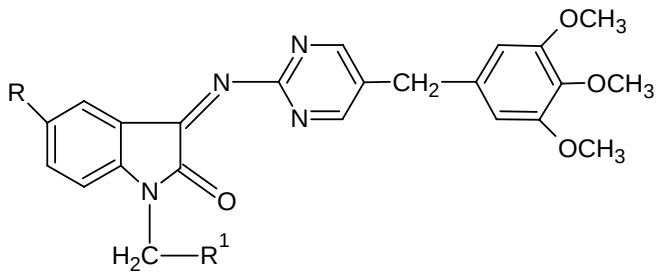


R^2= O, $NNHCOCH_3$, $NNHCH_3$,

$NNHCSNH_2$, NNHCOOH

R^3= H , NO_2

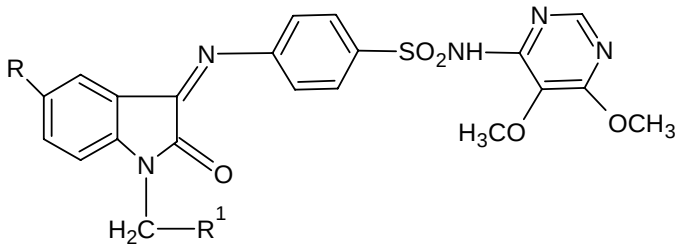
32. **Pandeya and Sriram** synthesized isatin and its derivatives with trimethoprim and their N- Mannich Bases.[39]



R = H , CH_3

R^1= -$N(CH_3)_2$, -$N(C_2H_5)_2$,-morpholino, -piperidino, -pyrrolidino, -sulphamethoxazolo

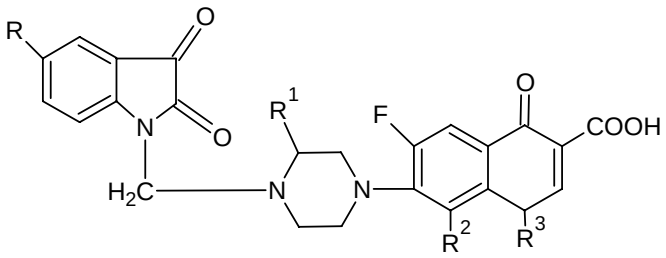
33. **Pandeya et.al.,** synthesized Schiff bases of isatin with sulfodoxine.[40]



R = H , CH3

R^1= N(CH3)2 , N(C2H5)2, 1-piperidyl, 1-pyrrolidinyl, 4-morpholinyl , pyrimethamine.

34. **Pandeya** synthesized isatin N-Mannich bases of Ciprofloxacin and Lomefloxacin.[41]

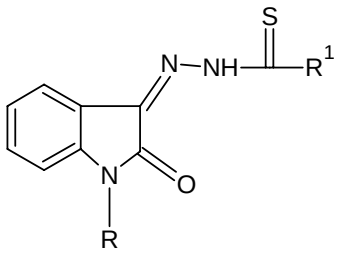


R = R^1 = H, CH_3

R^2=H, F

R^3= C_2H_5 , Cyclopropyl

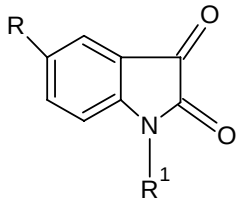
35. **Teitzs et.al. ,** synthesized substituted Isatin thiosemicarbazone and screened for antiviral activity.[42]



R = -CH3 , -CH2-CH=CH2

R^1= -N(C2H5)2, -N(CH2CH=CH2)2

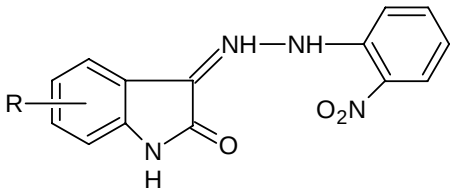
36. **Webber et al.,** reported the design, synthesis and biological evaluation of novel Isatin derivatives.[43]



R= H, Cl, NO_2, COOH, $COCH_3$, CN, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CSNH_2COCH_3$, $OSCH_3$

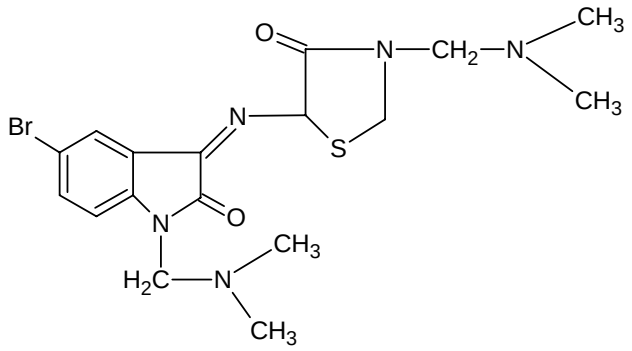
R^1= CH_3, CH_2-CH=CHC_6H_5, $CH(CH_2)_3$, C_6H_5,$CH_2C_6H_5$,CH_2, CH_2-β-naphthyl, $CH_2(4\text{-}CH_3\text{-}C_6H_4)$, $CH_2(3,4\text{-}(CH_3)_2\text{-}C_6H_3)$,$CH_2(3\text{-}OCH_3\text{-}C_6H_4)$, $CH_2(3,5\ (OCH_3)_2\text{-}C_6H_3)$

37**. F.D. Popp et al.,** synthesized 3-(o)-nitro phenyl hydrazones of isatin derivatives and screened for Anticancer activity.[44]

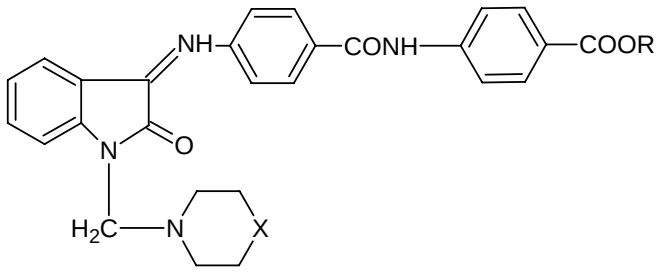


R = -H, 1-CH_3, 1-$COCH_3$, 4-CF_3, 5-Br, 5-Cl, 5-F, 5-OCH_3, 5-CH_3, 5-NO_2, 5-SO_3H, 7-Cl, 7-CH_3, 4Cl-7-OCH_3, 6-Cl-5-OCH_3, 4-Cl-7-CH_3, 4,7-$(Cl)_2$, 5,7-$(Cl)_2$, 4, 7-$(CH3)_2$, 5,7-$(CH3)_2$, 6,7-$(CH3)_2$

38. **Eshba and Salama** synthesized 5-(2-oxo,3-indolinyl)thiazolidine, 2,4-dione having Position1 and 3 of the Isatin and Thiazolindine rings respectively,substituted by Mannich bases.[45]



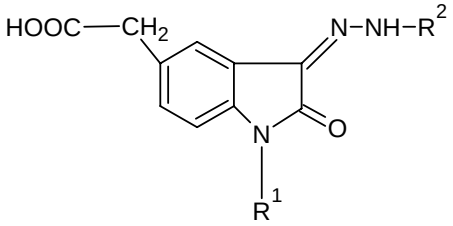
39. **Varma et.al.,** synthesized 3[p-(p-alokoxy carbonyl)-phenyl]imino-1-aminomethyl-2 indolinones and Investigated their antitubercular activity against Mycobacterium tuberculosis $H_{37}Rv$.[46]



X = O, CH_2,

R = CH_3, C_2H_5, n-propyl, n-butyl

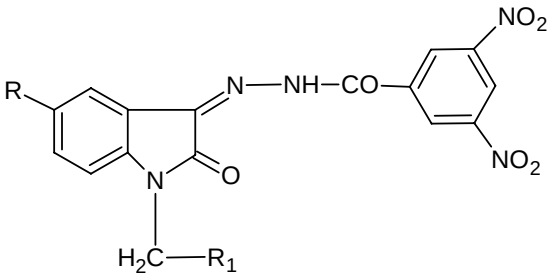
40. **Rajendra S.Varma etal.,** synthesized 1,3 disubstituted 5-carboxy methyl -2-indolinone as CNS active agents.[47]



R^1= H, CH3, Morpholinylmethyl, piperidino methyl

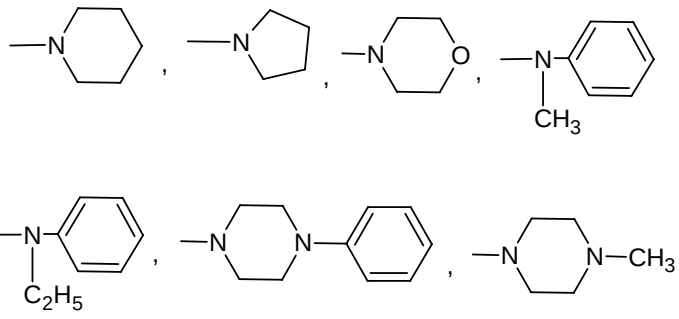
R^2= benzoyl, phenyl aminothiocarbonyl, p-(Cl)benzoyl, p-(OH)benzoyl

41. **Alka pande et al.,** synthesized 1, 3 disubstituted new indole derivatives as antiviral agents.[48]

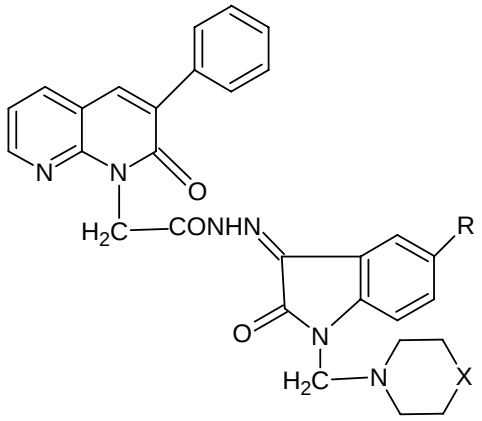


R = CH_3, Br

R1= -N(CH3)2, -N-(C2H5)2, -N(CH2OH)2,

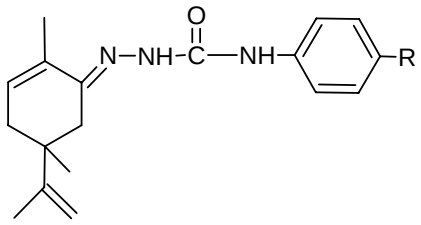


42. **K.Mugilaiah et al.,** synthesized novel Isatin Mannich bases bearing 1, 8 – naphthyridin Moiety.[49]

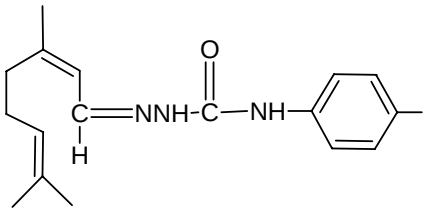


R= H, CH_3, Cl, Br X= CH_2, O, N-CH_3

43. **Navneet Agarwal et al**., synthesized 4-aryl substituted semicarbazones of some terpenes as Novel anticonvulsants.[50]

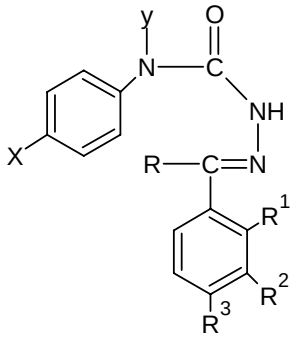


R= H, Cl, Br, F, CH_3, OCH_3, NO_2



R= H, Cl, Br, F, CH_3, OCH_3, NO_2

44. S.N Pandeya, synthesized 4-N substituted aryl semicarbazones as anticonvulsant agents.[51]

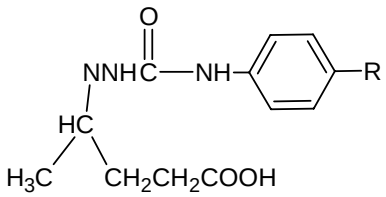


X= H, Cl, NO2 y = -C2H5, -H

R= H, CH_3 R^1= -OH, -H, -Cl

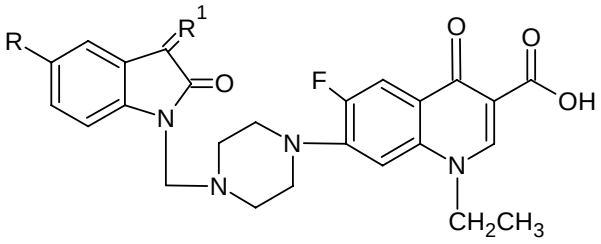
R^2= H,OCH_3 R^3= H,-OH,-OCH_3, NO_2

45. Navneet Agarwal et.al., synthesized 4-substituted semicarbazones of Levulenic acid & evaluated for anticonvulsant activity.[52]

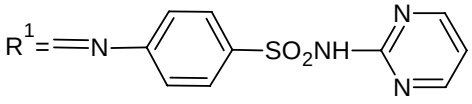


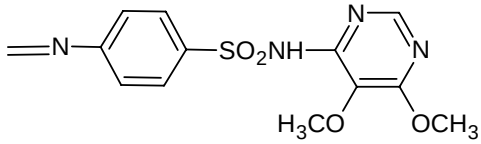
R= H, Cl, Br, F, CH_3, OCH_3, NO_2

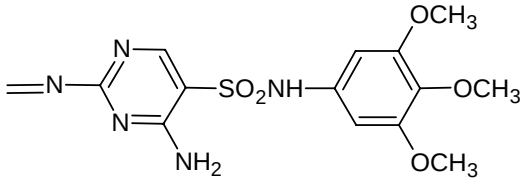
46. Surendra N. Pandeya, Dhamrajan Sriram et al., synthesized norfloxacin Mannich bases and Evaluated the antibacterial, antifungal and anti-HIV activities.[53]



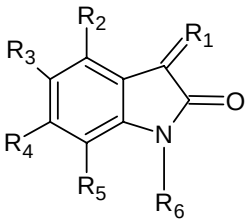
R= H, Cl, Br





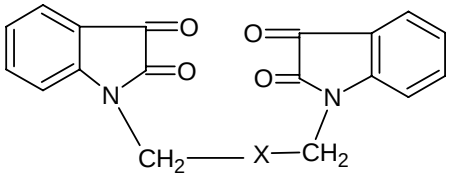


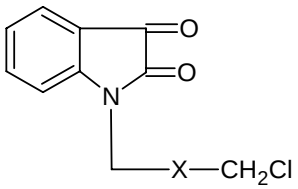
47. Kara L. Vine, Julie M. Locke, Marie Ranson, Stephen G. Pyneb and John B. Bremnerb Carry out the In vitro cytotoxicity evaluation of some substituted isatin derivatives.[54]

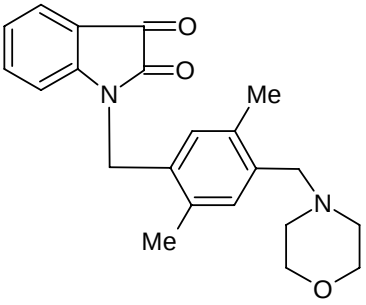


R_1, R_2, R_3, R_4, R_5, R_6 = H, CH

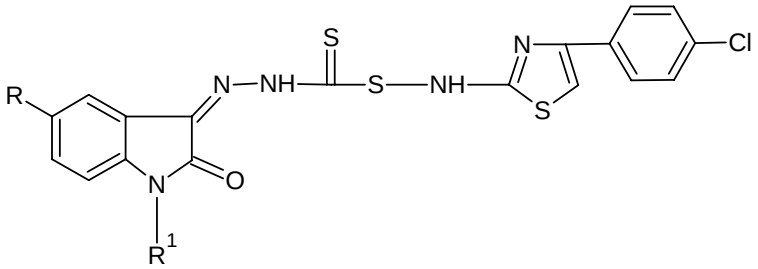
48. E.G. Mesropyan, G.B. Ambartsumyan, A.A. Avetisyan, M.G. Sargsyan, and A.S. galstyan, Synthesis of new isatin aromatic derivatives.[55]



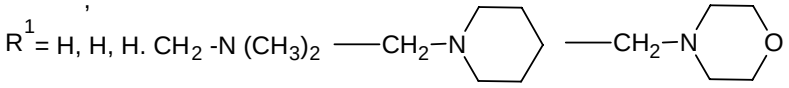




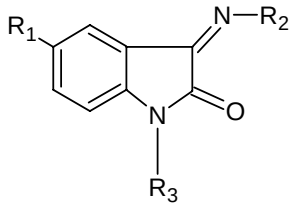
49. S.N. Pandeya, D. Sriram, G. Nath, E. DeClercq, Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and *N*-[4-(49-chlorophenyl) thiazol-2-yl] thiosemicarbazide.[56]



R = H , Cl, Br,



50. Seshaiah Krishnan Sridhar, Surendra N. Pandeya, James P. Stables, Atmakuru Ramesh, Study the Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives.[57]



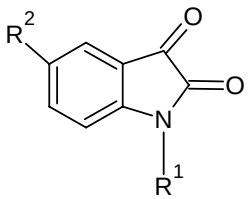
R^1= H, H, H, H, H, H, H

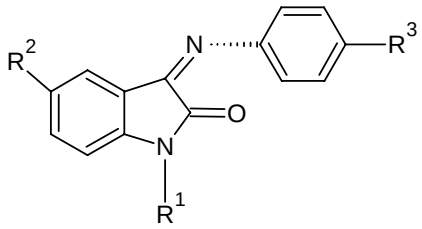
R^2= 1-Napthyl, 4- Chloro penyl, 4- Methyl Phenyl, 4- Bromo phenyl

4- Methoxy phenyl, Thiosemi carbazino, Phenyl Hydrazino

R^3= H, H, H, H, H, H, H

51. Asensio González , Josefina Quirante et al., Synthesis of Isatin derivatives, a novel class of transthyretin fibrillogenesis inhibitors.[58]



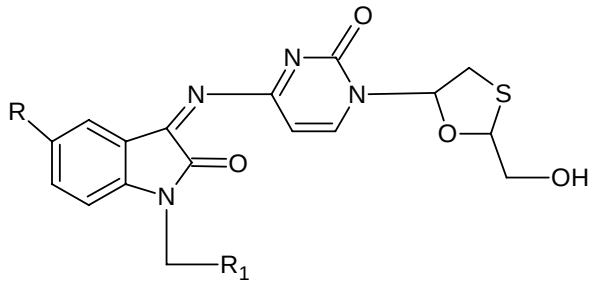


R^1= H, CH_3,H, CH_3, H, CH_3

R^2= H, H, H, H, I

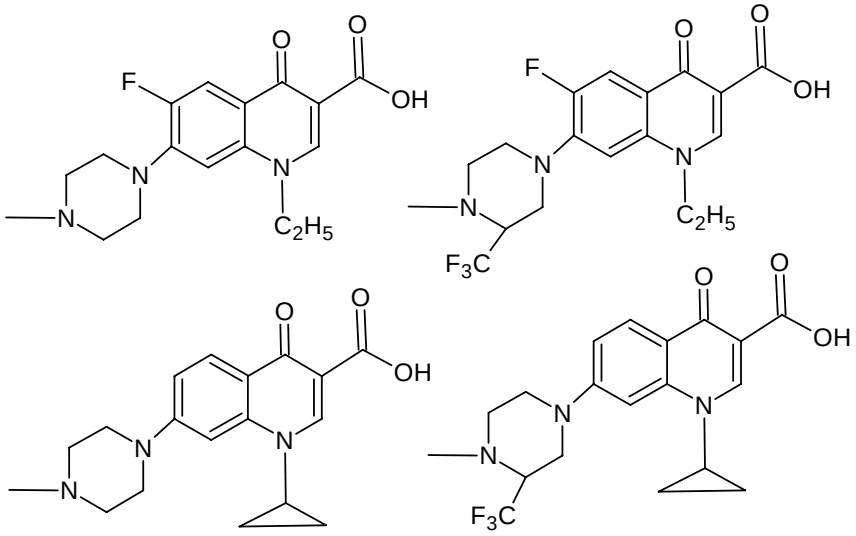
R^3= H, H, H, H, H, CH_3.

52. Dharmarajan Sriram, PerumalYogeeswari, Gayatri Gopal, Synthesis, anti-HIV and antitubercular activities of lamivudine prodrugs.[59]



R= H, Cl, F

R_1=



OBJECTIVE OF THE PRESENT WORK

Based on the literature review, Isatin nucleus has attracted the attention of medicinal chemists due to the wide range of biological activities.

Basic Structure of Isatin [5, 61]

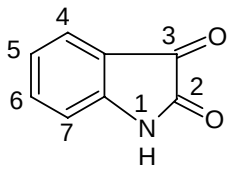


Fig-1

Structural Modifications involving variations in the nature of groups in Keto position (C=O) have led to a larger number of derivatives by Schiff's Reaction that are biologically active.

Most of the Isatin derivatives having substitutions at C-3 and C-1 positions having wide range of biological activities[6] (Fig-1)

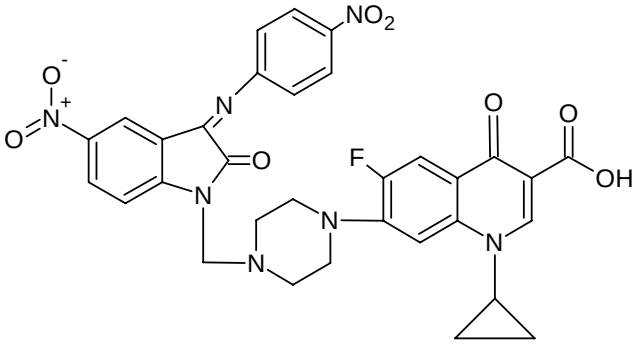
So, in this present study I aimed to synthesis some Novel Schiff and Mannich bases of isatin derivatives and screened for its Anti Microbial, Analgesic and Ulcerogenic activities.

Schiff Bases can be prepared by using p-Nitro aniline, PABA, p-Bromo aniline and Sulphanilamide. Mannich base can be prepared by using Ciprofloxacin.

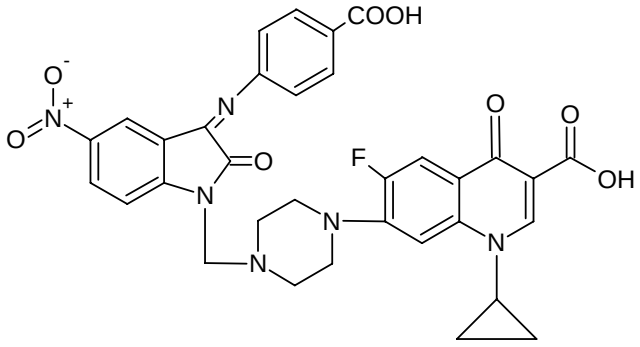
The objective of the present work can be summarized as follows.

I. Synthesis

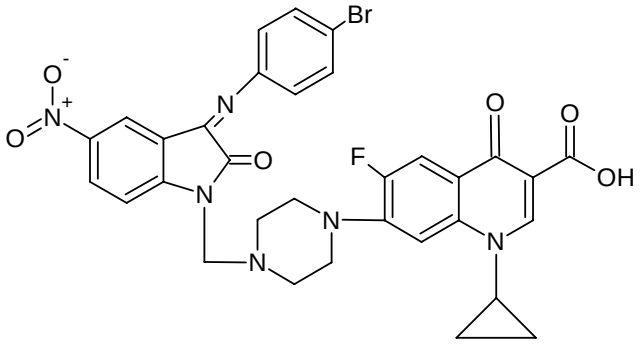
1. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'- nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



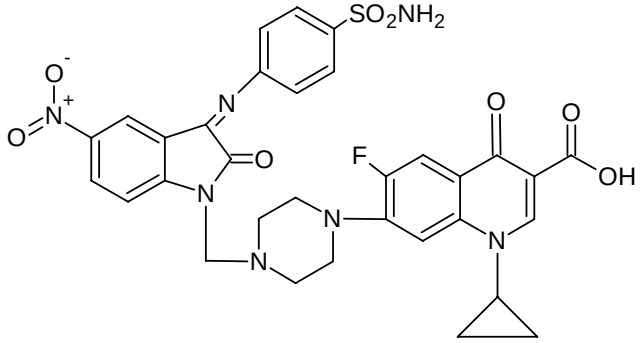
2. Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



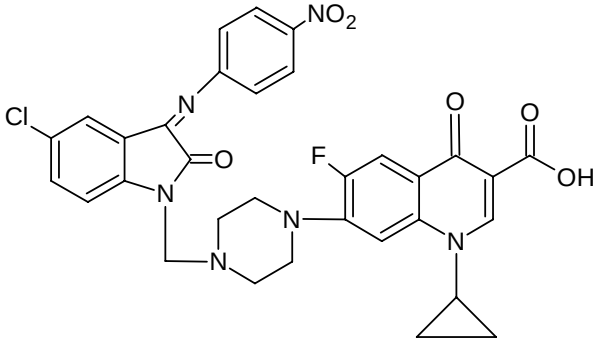
3. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



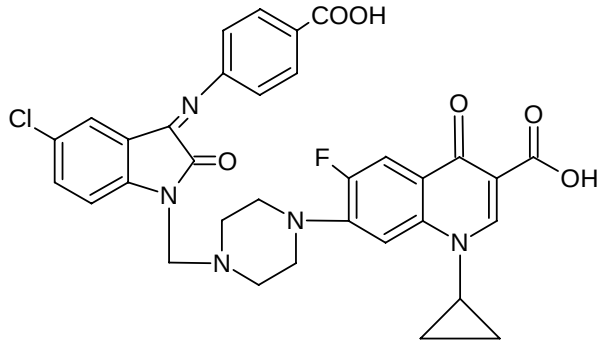
4. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



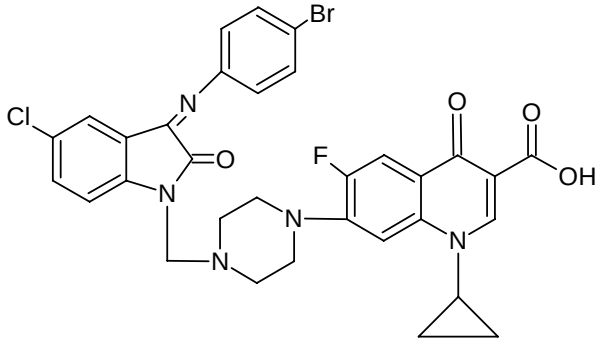
5. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5' chloro -3'-[(4'- nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



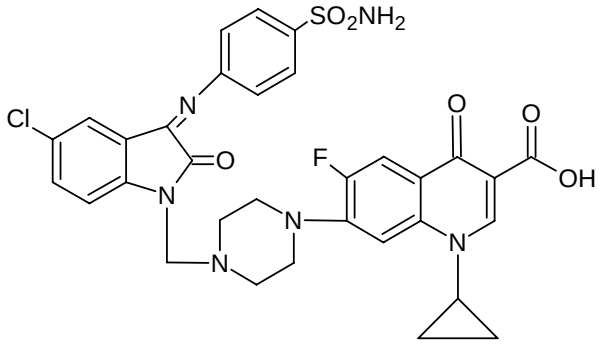
6. Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



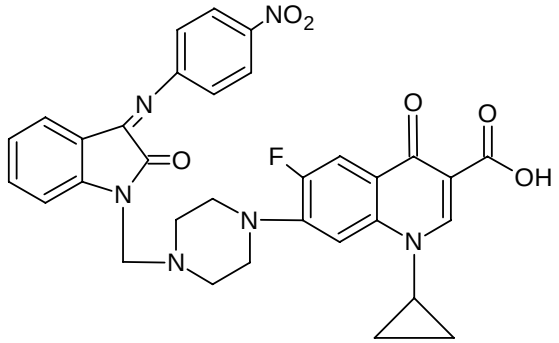
7. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid



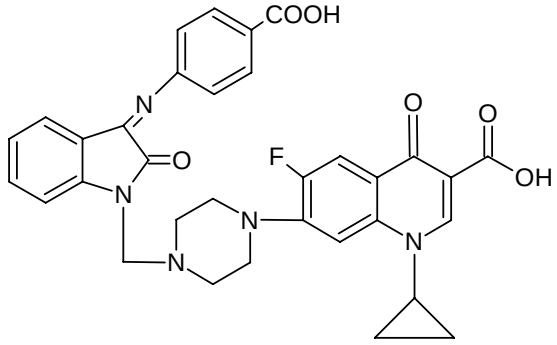
8. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



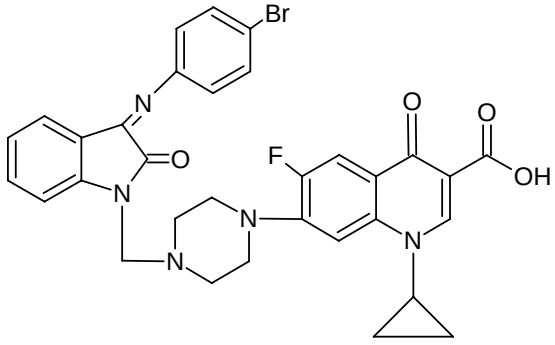
9. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



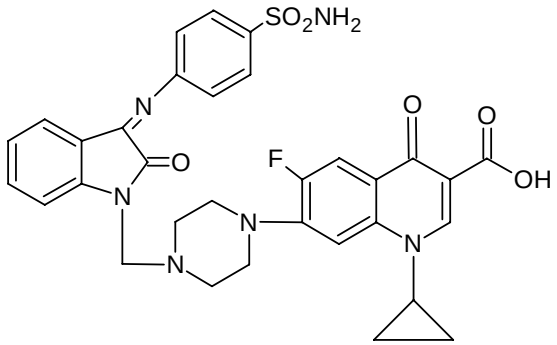
10. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



11. Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.



12. Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[3'-[(4'-Sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid



II. Characterization of the synthesized compounds by various analytical techniques like Melting Point, Thin Layer Chromatography, Infra Red Spectra and Nuclear Magnetic Resonance Studies.

III. A) Screening the synthesized compounds for Anti-Microbial Activity against the Micro Organisms such as *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Klebsilla aerogenes* and the fungi *Candida albicans* by Cup and Plate method.

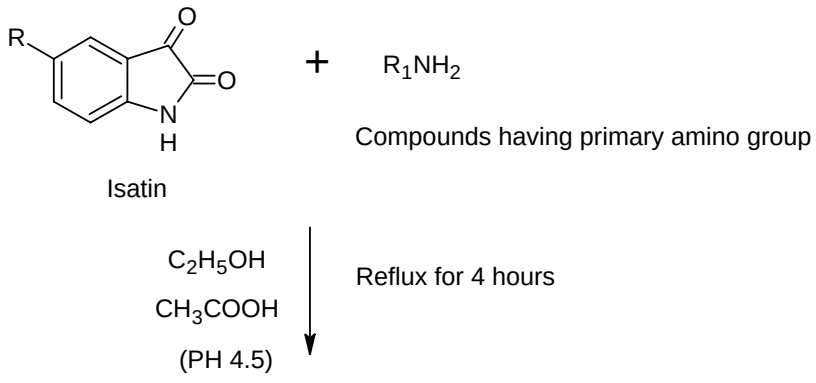
B) Evaluation of Analgesic activity for the synthesized compounds in mice using Diclofenac Sodium as standard drug by Acetic acid Induced Writhing Method.

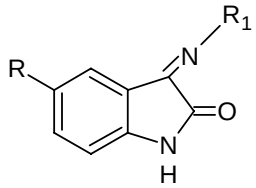
C) Evaluation of Ulcerogenic Index for the synthesized compounds in *Albino* rats.

GENERAL SCHEME OF REACTION

Synthesis of Schiff's bases of isatin: [23, 63]

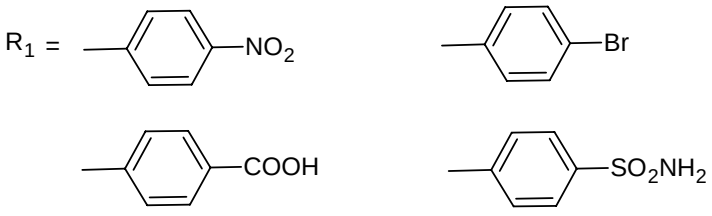
Step - I:





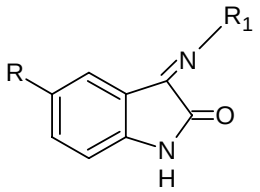
Schiff's Base of Isatin

R = NO_2, Cl, H



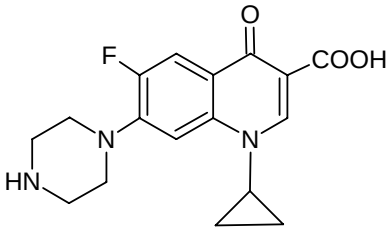
Synthesis of Mannich Bases of Isatin: [52, 60, 62, 63, 64]

Step - II:



Schiff's Bases of Isatin

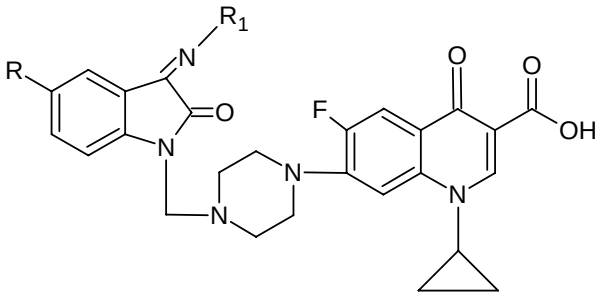
+



Ciprofloxacin

HCHO
(37 to 41% Formalin)

Mannich Reactions



Schiff's and Mannich Bases of Isatin

SYNTHESIS

I) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 5-nitro-3-[(4-nitrophenyl) imino]-1, 3-dihydro-2*H*-indol-2-one.

CHEMICALS REQUIRED

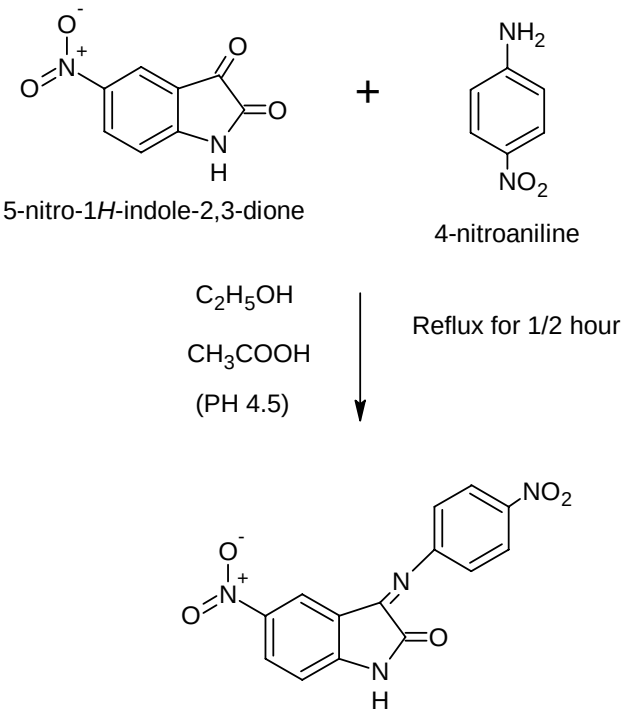
1) 5-Nitro Isatin - 0.01 mol
2) p-Nitro aniline - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

Equimolar quantities of 5- Nitro isatin (0.01 mol) and p-Nitro aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

SYNTHESIS OF 5-NITRO-3-[(4-NITROPHENYL) IMINO]-1,3-DIHYDRO-2H-INDOL-2-ONE:

Step - I:



5-nitro-1*H*-indole-2,3-dione + 4-nitroaniline

5-nitro-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-nitro phenyl) - imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

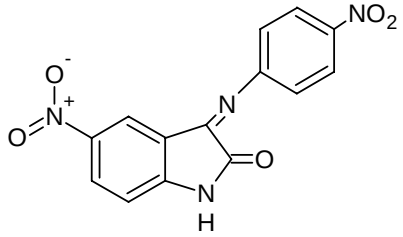
1) 5-nitro-3-[(4-nitrophenyl) imino]-1,3-dihydro-2*H*-indol-2-one - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 5-nitro-3-[(4-nitrophenyl) imino]-1,3-dihydro-2*H*-indol-2-one (0.0025 mol) and 37% formalin(1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

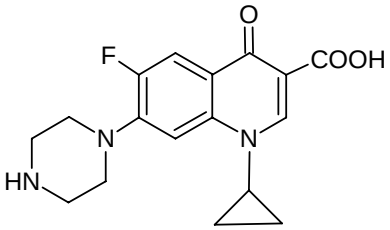
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[5'NITRO-3'-[(4'- NITRO PHENYL) - IMINO-1'-ISATINYL] METHYL] N^1 PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -II:



5-nitro-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

+



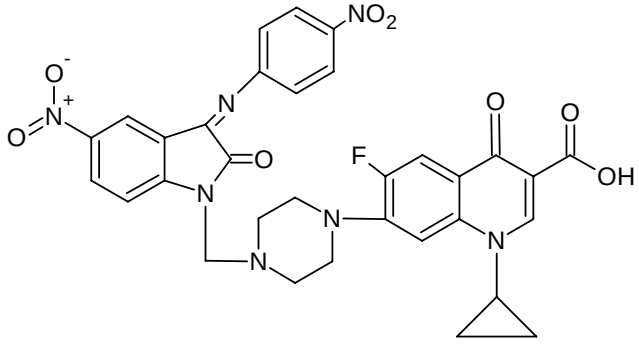
Ciprofloxacin

Glacial CH_3COOH

HCHO

(37% Formalin)

Mannich Reactions



Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'- nitro phenyl) - imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

II) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 4-[(5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] benzoic acid

CHEMICALS REQUIRED

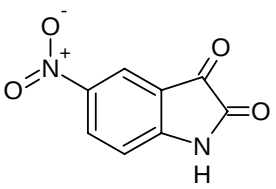
1) 5-Nitro Isatin - 0.01 mol
2) Para Amino Benzoic Acid - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

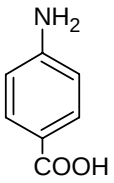
Equimolar quantities of 5- Nitro isatin (0.01 mol) and Para Amino Benzoic Acid (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

SYNTHESIS OF 4-[(5-NITRO-2-OXO-1,2-DIHYDRO-3H INDOL-3-YLIDENE) AMINO] BENZOIC ACID:

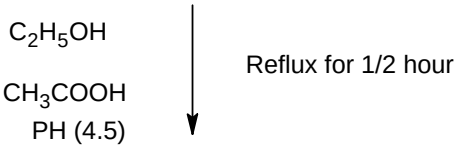
Step -I:

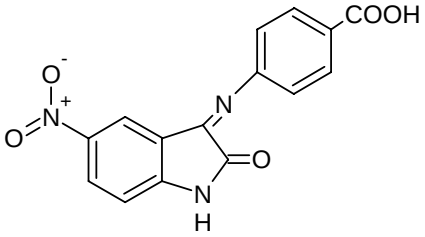


5-nitro-1*H*-indole-2,3-dione



4-aminobenzoic acid





4-[(5-nitro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzoic acid

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'carboxy phenyl) - imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

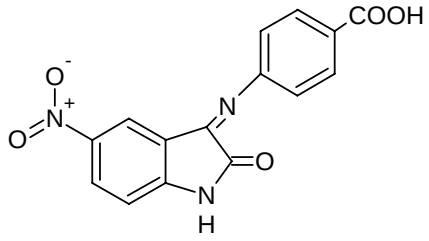
1) 4-[(5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene)amino]benzoic acid - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 4-[(5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] benzoic acid (0.0025 mol) and 37% formalin (1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

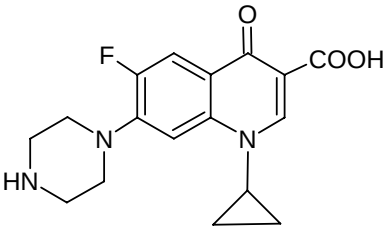
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO 7[[N^4-[5'-NITRO-3'-[(4'-CARBOXY PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -I:



4-[(5-nitro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzoic acid

+



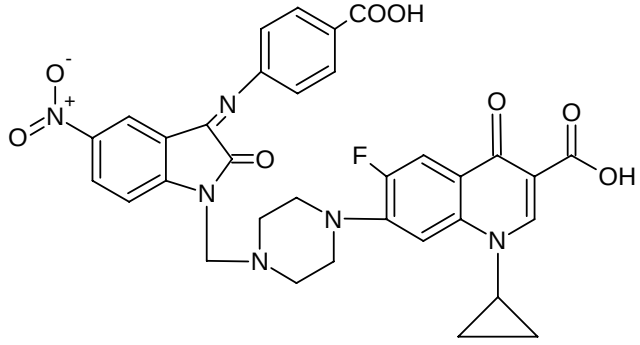
Ciprofloxacin

Glacial CH_3COOH

HCHO

(37% Formalin)

Mannich Reactions



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'-nitro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

III) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 3-[(4-bromophenyl) imino]-5-nitro-1, 3-dihydro-2*H*-indol-2-one

CHEMICALS REQUIRED

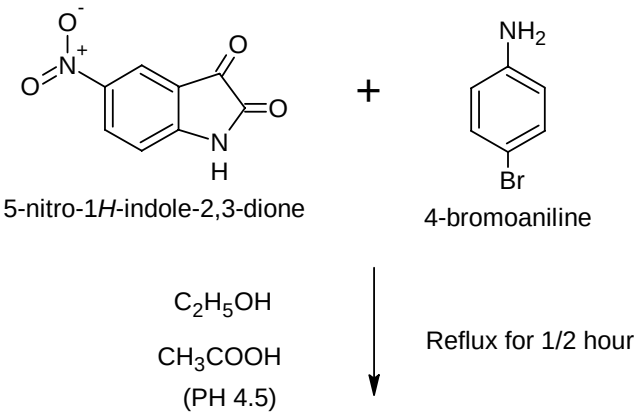
1) 5-Nitro Isatin - 0.01 mol
2) p-Bromo aniline - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

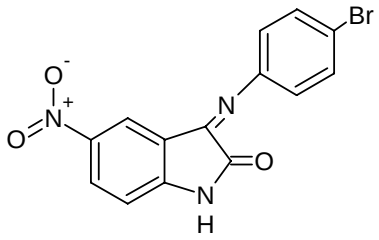
Equimolar quantities of 5- Nitro isatin (0.01 mol) and p-Bromo aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

SYNTHESIS OF 3-[(4-BROMOPHENYL) IMINO]-5-NITRO-1,3-DIHYDRO-2H INDOL-2-ONE:

Step -I:



5-nitro-1*H*-indole-2,3-dione + 4-bromoaniline



3-[(4-bromophenyl)imino]-5-nitro-1,3-dihydro-2*H*-indol-2-one

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

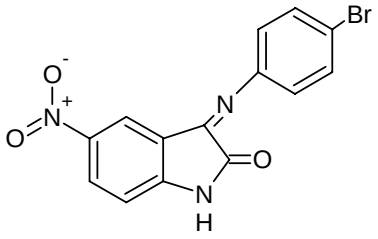
1) 3-[(4-bromophenyl)imino]-5-nitro-1,3-dihydro-2*H*-indol-2-one - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 3-[(4-bromophenyl)imino]-5-nitro-1,3-dihydro-2*H*-indol-2-one (0.0025 mol) and 37% formalin(1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

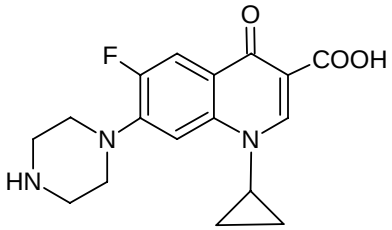
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[5'NITRO-3'-[(4'-BROMO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -II:



3-[(4-bromophenyl)imino]-5-nitro-1,3-dihydro-2*H*-indol-2-one

+



Ciprofloxacin

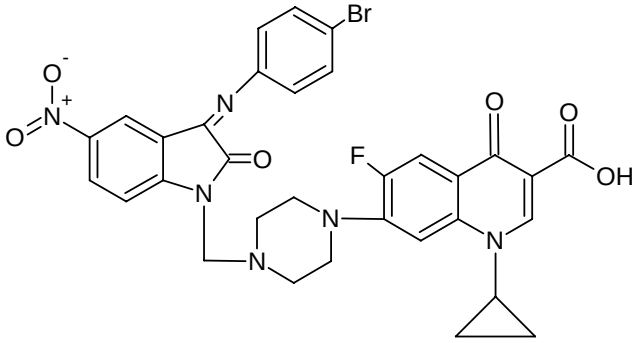
Glacial CH_3COOH

HCHO

(37% Formalin)

Reflux for 1 to 3 hrs

Mannich Reactions



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

IV) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 4-[(5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] benzenesulfonamide

CHEMICALS REQUIRED

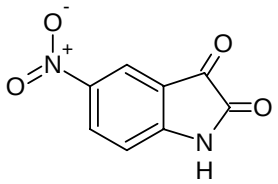
1) 5-Nitro Isatin - 0.01 mol
2) Sulphanilamide - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

Equimolar quantities of 5- Nitro isatin (0.01 mol) and Sulphanilamide (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

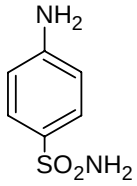
SYNTHESIS OF 4-[(5-NITRO-2-OXO-1,2DIHYDRO-3H-INDOL-3-YLIDINE) AMINO]BENZENESULPHONAMIDE:

Step -I:



5-nitro-1*H*-indole-2,3-dione

+



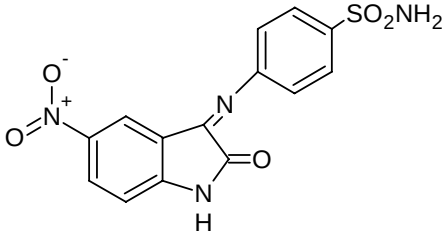
4-aminobenzenesulfonamide

C_2H_5OH

CH_3COOH

(PH 4.5)

Reflux for 1/2 hour



4-[(5-nitro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzenesulfonamide

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

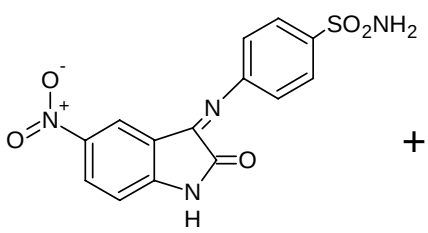
1) 4-[(5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] Benzenesulfonamide - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 4-[(5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] Benzenesulfonamide (0.0025 mol) and 37% formalin (1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

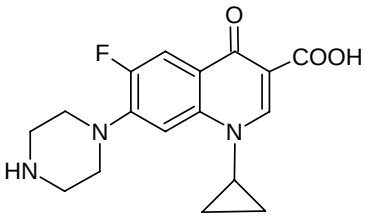
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[5'NITRO-3'-[(4' SULPHAMIDO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -II:



4-[(5-nitro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzenesulfonamide

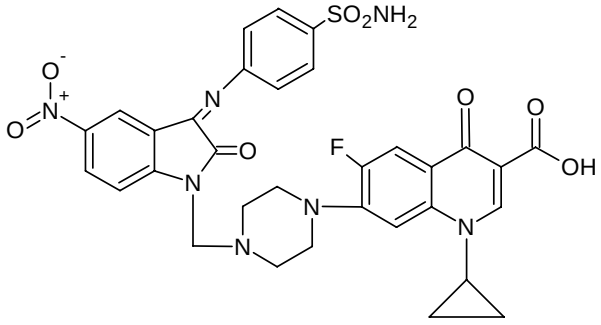
+



Ciprofloxacin

Glacial CH_3COOH
HCHO
(37% Formalin)

Mannich Reactions
Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

V) SYNTHESIS OF SCHIFF BASE.[23]

Step-I:

Synthesis of 5**-chloro-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one**

CHEMICALS REQUIRED

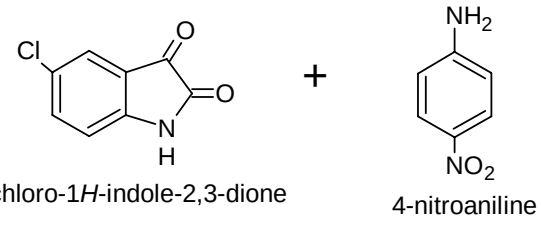
1) 5-Chloro Isatin - 0.01 mol
2) p-Nitro aniline - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

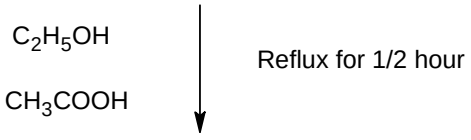
Equimolar quantities of 5- Chloro isatin (0.01 mol) and p-Nitro aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

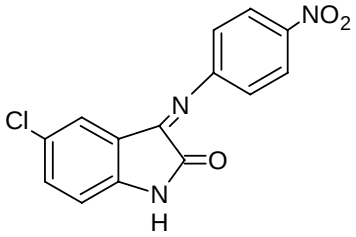
SYNTHESIS OF 5-CHLORO-3-[(4-NITROPHENYL)IMINO]-1,3-DIHYDRO -2H- INDOL-2-ONE:

Step -I:



5-chloro-1*H*-indole-2,3-dione 4-nitroaniline





5-chloro-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro -3'-[(4'-nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

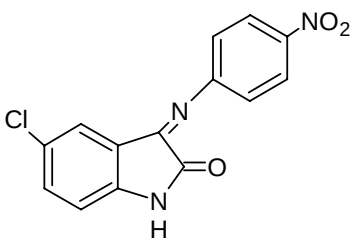
1) 5-chloro-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 5-chloro-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one (0.0025 mol) and 37% formalin(1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

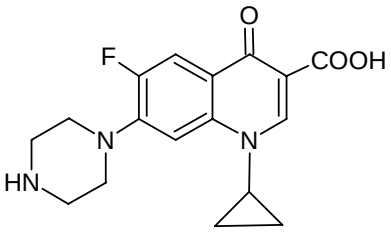
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[5'CHLORO -3'-[(4'- NITRO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -II:



5-chloro-3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

+



Ciprofloxacin

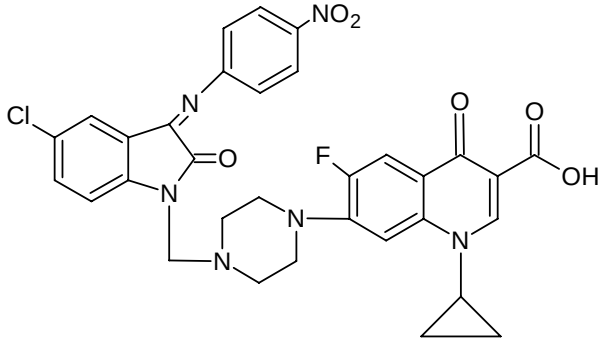
Glacial CH_3COOH

HCHO

(37% Formalin)

Mannich Reactions

Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro -3'-[(4'- nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

VI) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 4-[(5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3 ylidene)amino] benzoic acid

CHEMICALS REQUIRED

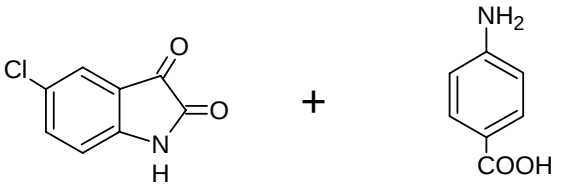
1) 5-Chloro Isatin - 0.01 mol
2) Para Amino Benzoic Acid - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

Equimolar quantities of 5- Chloro isatin (0.01 mol) and Para Amino Benzoic Acid (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

SYNTHESIS OF 4-[(5-CHLORO-2-OXO-1, 2-DIHYDRO-3*H*-INDOL-3 YLIDENE)AMINO] BENZOIC ACID:

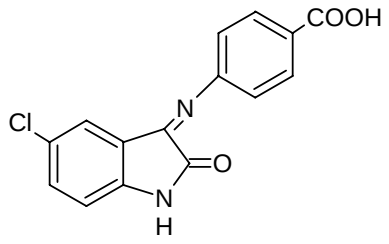
Step -I:



5-chloro-1*H*-indole-2,3-dione 4-aminobenzoic acid

C_2H_5OH
CH_3COOH
(PH 4.5)

Reflux for 1/2 hour



4-[(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzoic acid

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

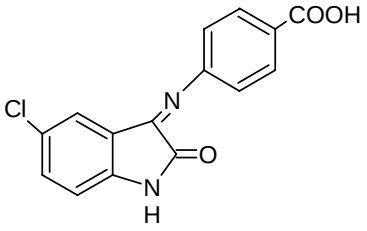
1) 4-[(5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3 ylidene) amino] benzoic acid - 0.0025mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 4-[(5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] benzoic acid (0.0025 mol) and 37% formalin (1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[5'CHLORO-3'-[(4'-CARBOXY PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -II:



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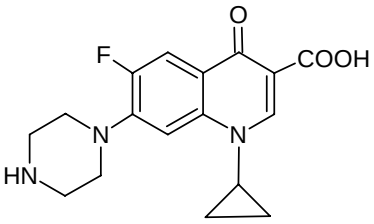


4-[(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzoic acid

Ciprofloxacin

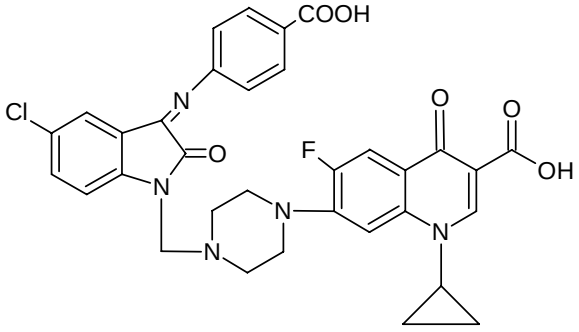
Glacial CH_3COOH

HCHO

(37% Formalin)

Mannich Reactions

Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'-chloro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

VII) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 3-[(4-bromophenyl)imino]-5-chloro-1,3-dihydro-2*H*-indol-2-one

CHEMICALS REQUIRED

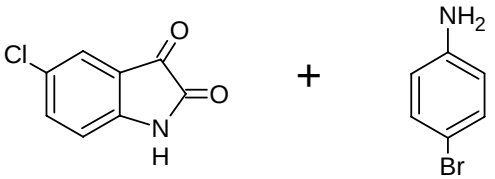
1) 5-Chloro Isatin - 0.01 mol
2) p-Bromo aniline - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

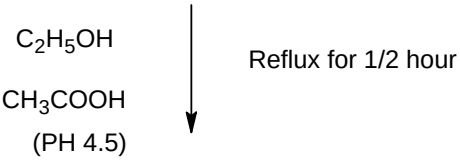
Equimolar quantities of 5- Chloro isatin (0.01 mol) and p-Bromo aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

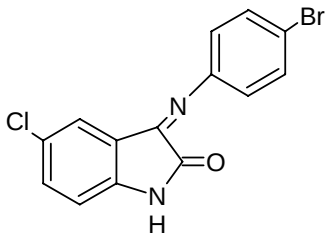
SYNTHESIS OF 3-[(4-BROMOPHENYL)IMINO]-5-CHLORO-1,3-DIHYDRO-2*H*-INDOL-2-ONE:

Step -I:



5-chloro-1*H*-indole-2,3-dione 4-bromoaniline





3-[(4-bromophenyl)imino]-5-chloro-1,3-dihydro-2*H*-indol-2-one

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

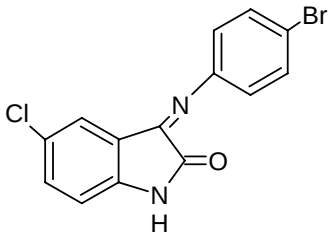
1) 3-[(4-bromophenyl)imino]-5-chloro-1,3-dihydro-2*H*-indol-2-one - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 3-[(4-bromophenyl)imino]-5-chloro-1,3-dihydro-2*H*-indol-2-one (0.0025 mol) and 37% formalin(1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

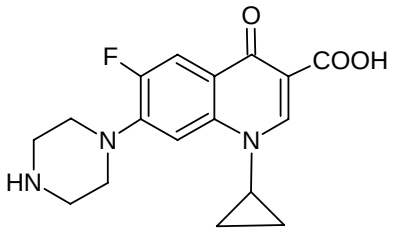
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[5'CHLORO-3'-[(4'-BROMO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID.

Step -II:



3-[(4-bromophenyl)imino]-5-chloro-1,3-dihydro-2*H*-indol-2-one

+



Ciprofloxacin

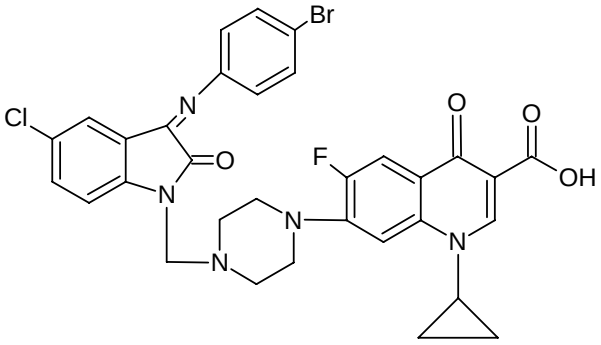
Glacial CH_3COOH

HCHO

(37% Formalin)

Mannich Reactions

Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

VIII) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 4-[(5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] benzenesulfonamide

CHEMICALS REQUIRED

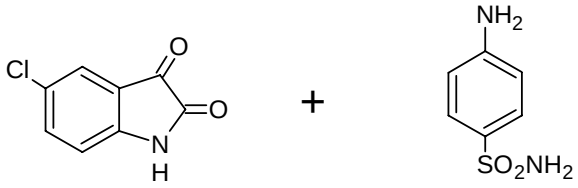
1) 5-Chloro Isatin - 0.01 mol
2) Sulphanilamide - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

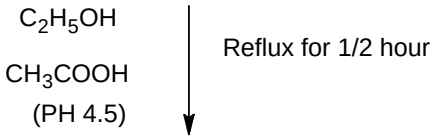
Equimolar quantities of 5- Chloro isatin (0.01 mol) and Sulphanilamide (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

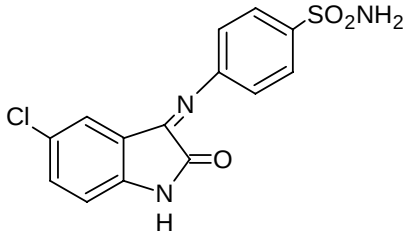
SYNTHESIS OF 4-[(5-CHLORO-2-OXO-1, 2-DIHYDRO-3*H*-INDOL-3-YLIDENE) AMINO] BENZENESULFONAMIDE:

Step -I:



5-chloro-1*H*-indole-2,3-dione + 4-aminobenzenesulfonamide





4-[(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzenesulfonamide

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

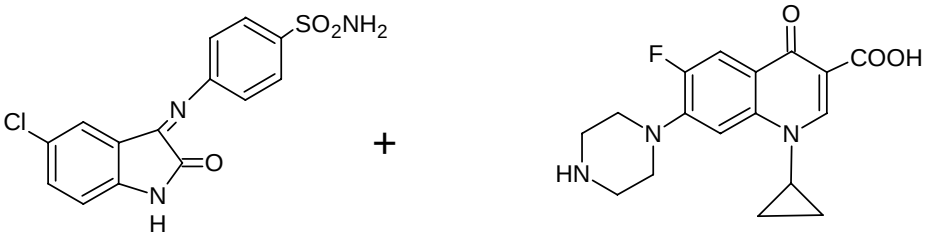
1) 4-[(5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] Benzenesulfonamide - 0.0025mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 4-[(5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] Benzenesulfonamide (0.0025 mol) and 37% formalin (1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[5'CHLORO-3'-[(4' SULPHAMIDO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

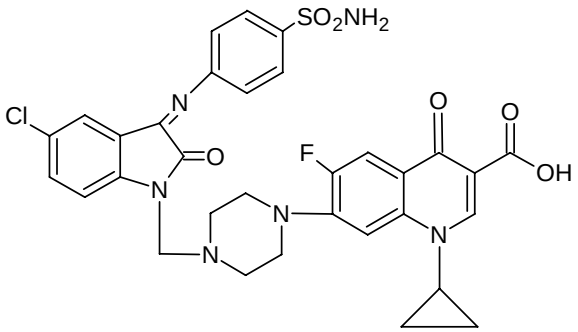
Step -I:



4-[(5-chloro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzenesulfonamide Ciprofloxacin

Glacial CH_3COOH
HCHO
(37% Formalin)

Mannich Reactions
Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

IX) SYNTHESIS OF SCHIFF BASE.[23]

Step-I:

Synthesis of 3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

CHEMICALS REQUIRED

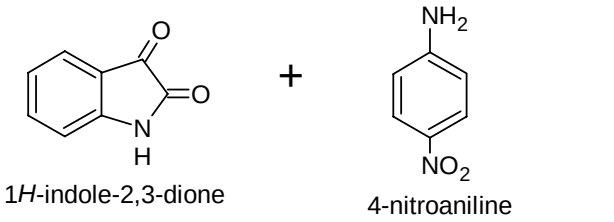
1) Isatin - 0.01 mol
2) p-Nitro aniline - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

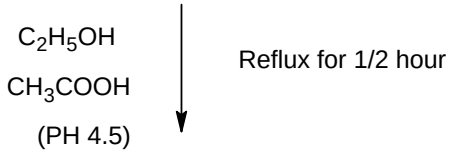
Equimolar quantities of Isatin (0.01 mol) and p-Nitro aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

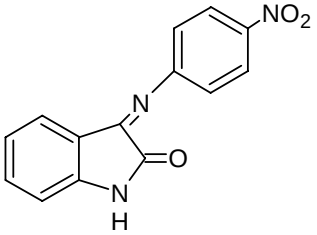
SYNTHESIS OF 3-[(4-NITROPHENYL)IMINO]-1,3-DIHYDRO-2*H*-INDOL-2-ONE:

Step -I:



1*H*-indole-2,3-dione 4-nitroaniline





3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'- nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

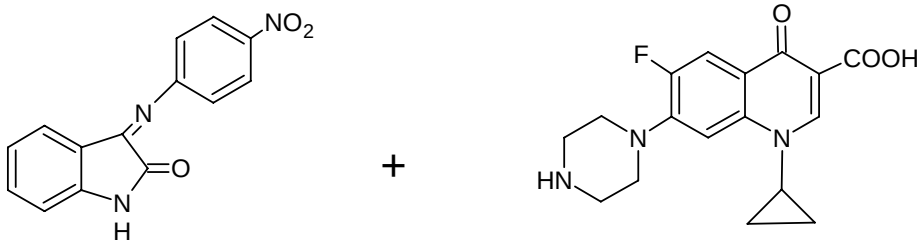
1) 3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one (0.0025 mol) and 37% formalin(1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[3'-[(4'- NITRO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

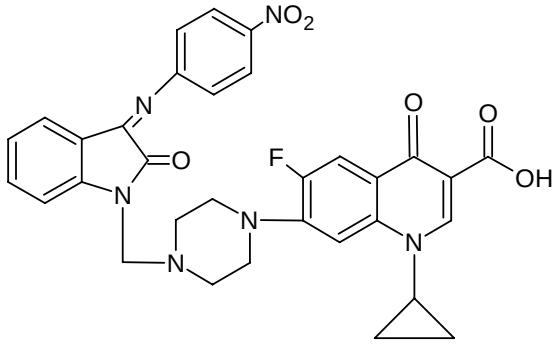
Step -II:



3-[(4-nitrophenyl)imino]-1,3-dihydro-2*H*-indol-2-one + Ciprofloxacin

Glacial CH_3COOH
HCHO
(37% Formalin)

Mannich Reactions
Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'- nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

X) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 4-[(2-oxo-1, 2-dihydro-3*H*-indol-3 ylidene) amino] benzoic acid

CHEMICALS REQUIRED

1) Isatin - 0.01 mol
2) Para Amino Benzoic Acid - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

Equimolar quantities of Isatin (0.01 mol) and Para Amino Benzoic Acid (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

SYNTHESIS OF 4-[(2-OXO-1, 2-DIHYDRO-3*H*-INDOL-3 YLIDENE) AMINO] BENZOIC ACID:

Step -I:

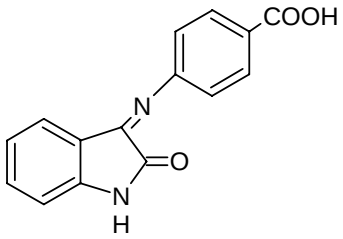
1*H*-indole-2,3-dione + 4-aminobenzoic acid

C_2H_5OH

CH_3COOH

(PH 4.5)

Reflux for 1/2 hour



4-[(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzoic acid

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

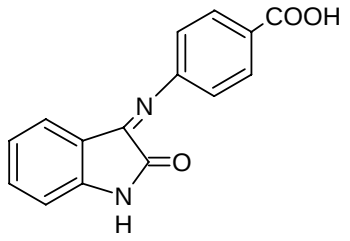
1) 4-[(2-oxo-1, 2-dihydro-3*H*-indol-3 ylidene) amino] benzoic acid - 0.0025mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 4-[(2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] benzoic acid (0.0025 mol) and 37% formalin (1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

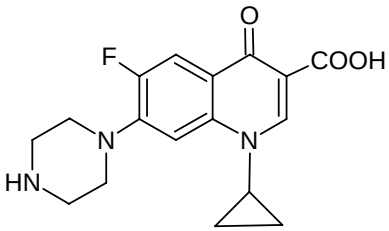
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[3'-[(4'-CARBOXY PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -I:



4-[(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzoic acid

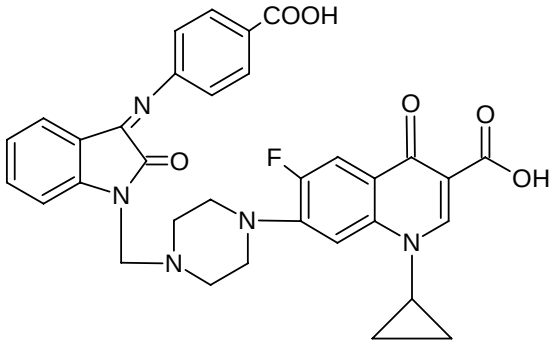
+



Ciprofloxacin

Glacial CH_3COOH
HCHO
(37% Formalin)

Mannich Reactions
Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

XI) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 3-[(4-bromophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

CHEMICALS REQUIRED

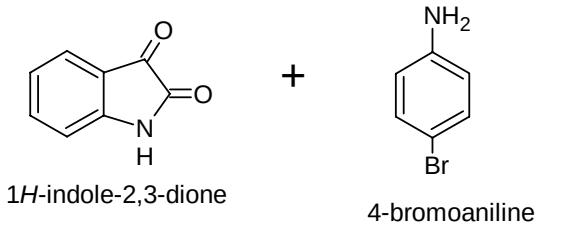
1) Isatin - 0.01 mol
2) p-Bromo aniline - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

Equimolar quantities of Isatin (0.01 mol) and p-Bromo aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

SYNTHESIS OF 3-[(4-BROMOPHENYL)IMINO]-1,3-DIHYDRO-2*H*-INDOL-2-ONE:

Step -I:



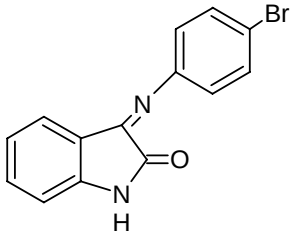
1*H*-indole-2,3-dione + 4-bromoaniline

C_2H_5OH

CH_3COOH

(PH 4.5)

Reflux for 1/2 hour



3-[(4-bromophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

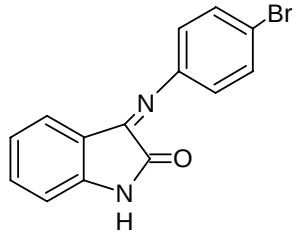
1) 3-[(4-bromophenyl)imino]-1,3-dihydro-2*H*-indol-2-one - 0.0025 mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 3-[(4-bromophenyl)imino]-1,3-dihydro-2*H*-indol-2-one (0.0025 mol) and 37% formalin(1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

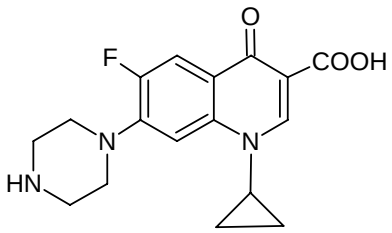
SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[3'-[(4'-BROMO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID:

Step -I:



3-[(4-bromophenyl)imino]-1,3-dihydro-2*H*-indol-2-one

+



Ciprofloxacin

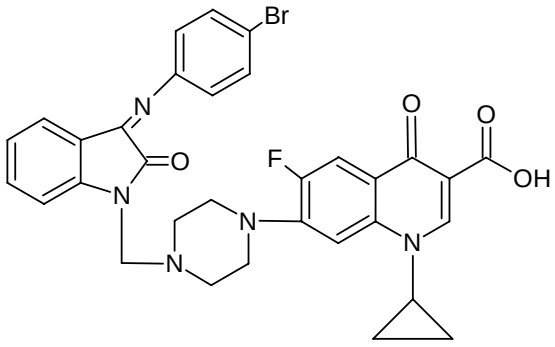
Glacial CH_3COOH

HCHO

(37% Formalin)

Mannich Reactions

Reflux for 1 to 3 hrs



Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

XII) SYNTHESIS OF SCHIFF BASE[23]

Step-I:

Synthesis of 4-[(2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] benzenesulfonamide

CHEMICALS REQUIRED

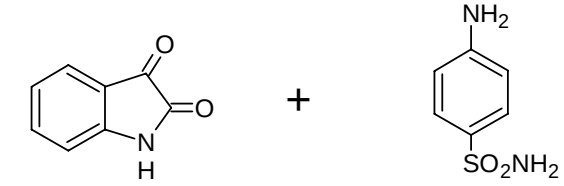
1) Isatin - 0.01 mol
2) Sulphanilamide - 0.01 mol
3) Ethanol - 20 ml
4) Glacial Acetic acid - 2 drops

PROCEDURE

Equimolar quantities of Isatin (0.01 mol) and Sulphanilamide (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

SYNTHESIS OF 4-[(2-OXO-1, 2-DIHYDRO-3*H*-INDOL-3-YLIDENE) AMINO] BENZENESULFONAMIDE:

Step -I:



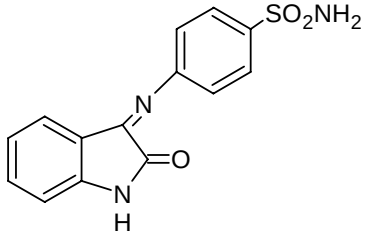
1*H*-indole-2,3-dione + 4-aminobenzenesulfonamide

C_2H_5OH

CH_3COOH

(PH 4.5)

Reflux for 1/2 hour



4-[(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzenesulfonamide

SYNTHESIS OF MANNICH BASE [52]

Step: 2

Synthesis of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

CHEMICALS REQUIRED

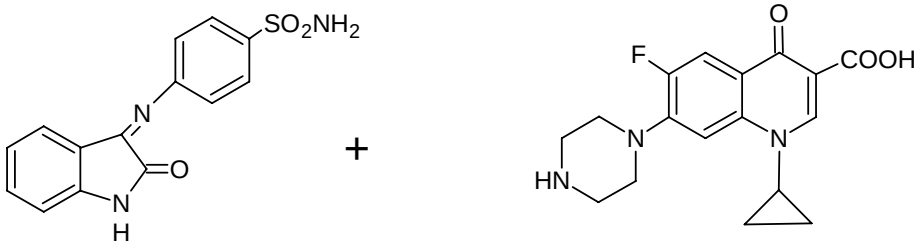
1) 4-[(2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] Benzenesulfonamide - 0.0025mol
2) Ciprofloxacin - 0.0025 mol
3) Glacial Acetic acid - 20 ml
4) 37% Formalin - 1 ml

PROCEDURE

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added 4-[(2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene) amino] Benzenesulfonamide (0.0025 mol) and 37% formalin (1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

SYNTHESIS OF 1-CYCLOPROPYL-6-FLUORO-1, 4-DIHYDRO-4-OXO-7[[N^4-[3'-[(4'SULPHAMIDO PHENYL)-IMINO-1'-ISATINYL] METHYL] N^1-PIPERAZINYL]-3-QUINOLINE CARBOXYLIC ACID.

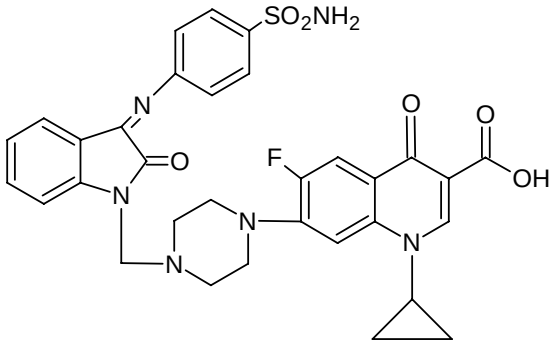
Step -II:



4-[(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]benzenesulfonamide Ciprofloxacin

Glacial CH_3COOH
HCHO
(37% Formalin)

Mannich Reactions
Reflux for 1 to 3 hrs



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

PHYSICAL DATA OF TITLED COMPOUNDS
Table No :1

Compound Code	Chemical Name	Molecular Formula	Molecular Weight (grams)	Percentage Yield
AS	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{26}FN_7O_8$	655.589	94.05%
A1S	1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{33}H_{27}FN_6O_8$	654.601	92.86%
A2S	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{26}BrFN_6O_6$	689.488	92.08%
A3S	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{28}FN_7O_8S$	689.670	94.87%
BS	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5' chloro -3'-[(4'- nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{26}ClFN_6O_6$	645.037	94.14%
B1S	1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{33}H_{27}ClFN_5O_6$	644.049	95.27%

PHYSICAL DATA OF TITLED COMPOUNDS

Compound Code	Chemical Name	Molecular Formula	Molecular Weight (grams)	Percentage Yield
B2S	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{26}BrClFN_5O_4$	678.935	92.99%
B3S	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4' sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{28}ClFN_6O_6S$	679.118	95.88%
CS	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{27}FN_6O_6$	610.592	98.36%
C1S	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{33}H_{28}FN_5O_6$	609.604	97.83%
C2S	1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.	$C_{32}H_{27}BrFN_5O_4$	644.490	94.38%
C3S	1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[3'-[(4'-Sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid	$C_{32}H_{29}FN_6O_6S$	644.673	95.09%

MELTING POINT ANALYSIS

Melting point was found in an open end capillary tube method by electrically heating melting point apparatus.

The melting point of synthesized compounds is given in the table no:2

Table No :2

S.NO	COMPOUND	MELTING POINT ^{0}C
1.	AS	126-129
2.	A1S	124-128
3.	A2S	142-145
4.	A3S	134-138
5.	BS	115-118
6.	B1S	136-138
7.	B2S	151-155
8.	B3S	141-143
9.	CS	124-126
10.	C1S	131-134
11.	C2S	147-151
12.	C3S	159-162

THIN LAYER CHROMATOGRAPHY ANALYSIS

Thin layer chromatography analysis was carried out by using Silica gel G (0.5mm thickness) coated over glass plate (12x20cm) as stationary phase, Chloroform: Methanol (9:1) as mobile phase, the spots were visualized by iodine vapours.

The Rf value of the synthesized compounds are given in the table no:3

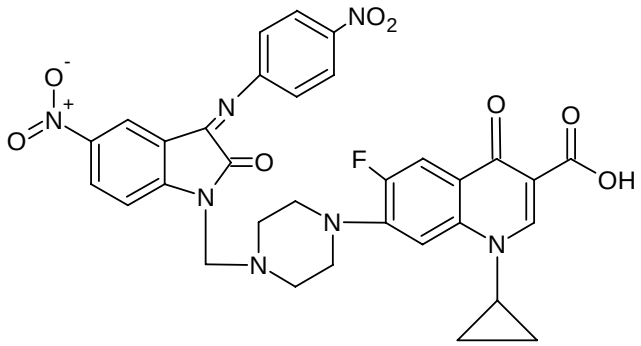
Table No: 3

S.No	COMPOUND	Rf VALUE
1.	AS	0.7846
2.	A1S	0.7941
3.	A2S	0.7969
4.	A3S	0.7681
5.	BS	0.8833
6.	B1S	0.8095
7.	B2S	0.7857
8.	B3S	0.8000
9.	CS	0.8750
10.	C1S	0.9077
11.	C2S	0.8281
12.	C3S	0.8593

INFRA RED SPECTRAL ANALYSIS [65-71]

The structure of the synthesized compounds was elucidated by PERKIN-ELMER FT-IR spectrophotometry using potassium bromide disc. The infra red values were measured as wave number in cm^{-1} and the results are shown below.

AS

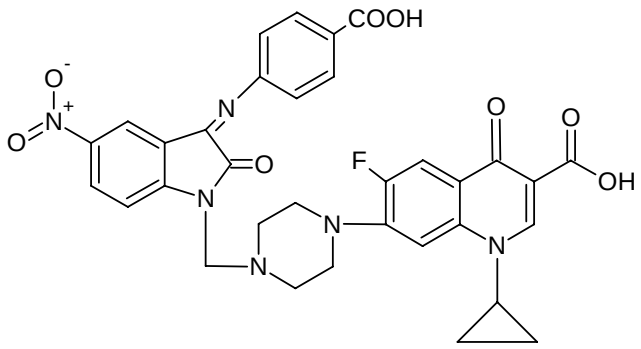


1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1695.65 cm^{-1}
3. C=N Stretching Vibration - 1635.10 cm^{-1}
4. C=C Aryl Stretching Vibration - 1590.26 cm^{-1}
5. =NH imino Stretching Vibration - 3320.85 cm^{-1}
6. Aromatic nitro group - 1550.26 & 1350.73 cm^{-1}
7. Para substitution in benzene ring - 832.39 cm^{-1}
8. Methylene bridge - 2934.33 cm^{-1}
9. Cyclo propane Stretching Vibration - 3050.30 cm^{-1}
10. C-F Stretching Vibration - 1030.07 cm^{-1}
11. Carboxylic acid Stretching Vibration- 2596.59 cm^{-1}
12. OH bending vibration for COOH - 945.03 cm^{-1}

A_1S

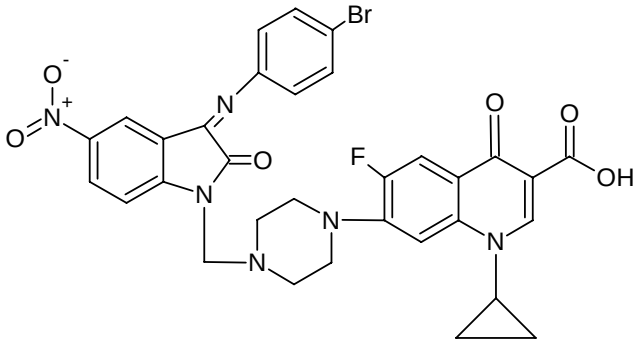


1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1677.51 cm^{-1}
3. C=N Stretching Vibration - 1595.69 cm^{-1}
4. =NH imino Stretching Vibration - 3352.86 cm^{-1}
5. Aromatic nitro group - 1330.57 cm^{-1}
6. Para substitution in benzene ring - 832.24 cm^{-1}
7. Methylene bridge - 2925.47 cm^{-1}
8. Cyclo propane Stretching Vibration - 3082.33 cm^{-1}
9. C-F Stretching Vibration - 1048.12 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2856.66 cm^{-1}
11. OH bending vibration for COOH - 964.50 cm^{-1}

A_2S

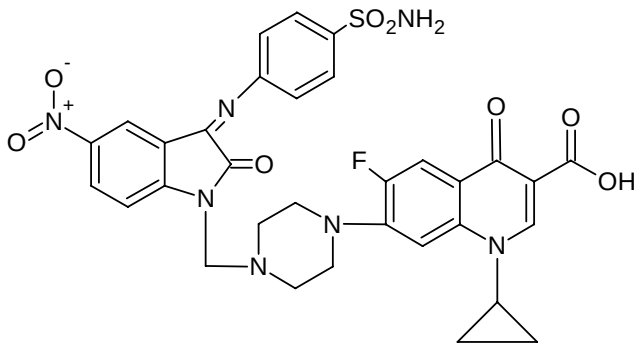


1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-bromophenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1745.26 cm^{-1}
3. C=N Stretching Vibration - 1641.22 cm^{-1}
4. C=C Aryl Stretching Vibration - 1615.05 cm^{-1}
5. =NH imino Stretching Vibration - 3412.25 cm^{-1}
6. Aromatic nitro group - 1350.56 cm^{-1}
7. Para substitution in benzene ring - 835.26 cm^{-1}
8. Methylene bridge - 2924.54 cm^{-1}
9. Cyclo propane Stretching Vibration - 3053.98 cm^{-1}
10. C-F Stretching Vibration - 1035.96 cm^{-1}
11. Carboxylic acid Stretching Vibration- 2501.53 cm^{-1}
12. OH bending vibration for COOH - 954.87 cm^{-1}
13. C-Br Stretching Vibration - 592.45 cm^{-1}

A_3S

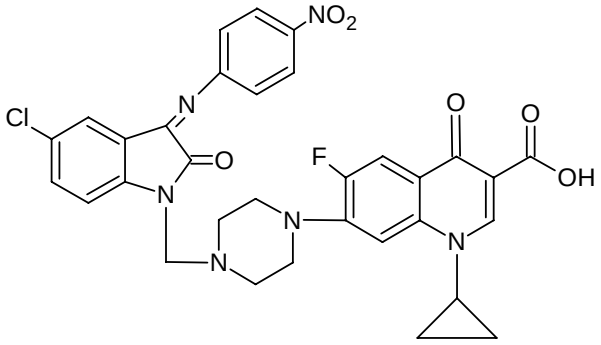


1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-Sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1721.16 cm^{-1}
3. C=N Stretching Vibration - 1638.77 cm^{-1}
4. C=C Aryl stretching Vibration - 1603.55 cm^{-1}
5. NH Asymmetric Stretching Vibration - 3356.89 cm^{-1}
6. Para substitution in benzene ring - 858.43 cm^{-1}
7. Methylene bridge - 2930.33 cm^{-1}
8. Cyclo propane Stretching Vibration - 3053.98 cm^{-1}
9. C-F Stretching Vibration - 1096.18 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2515.87 cm^{-1}
11. S-N Stretching Vibration - 901.33 cm^{-1}
12. SO_2 Asymmetric Stretching Vibration- 1332.66 cm^{-1}
13. SO_2 Symmetric Stretching Vibration - 1155.23 cm^{-1}
14. Aromatic NO_2 group - 1540.15 cm^{-1}

BS

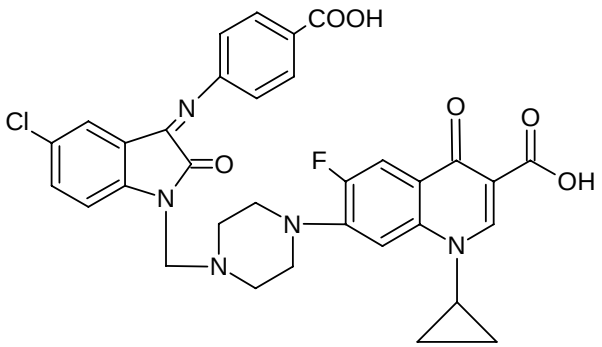


1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1742.37 cm^{-1}
3. C=N Stretching Vibration - 1678.84 cm^{-1}
4. C=C Aryl Stretching Vibration - 1597.22 cm^{-1}
5. =NH imino Stretching Vibration - 3364.94 cm^{-1}
6. Aromatic nitro group - 1354.26 cm^{-1}
7. Para substitution in benzene ring - 830.65 cm^{-1}
8. Methylene bridge - 2924.73 cm^{-1}
9. Cyclo propane Stretching Vibration - 3062.09 cm^{-1}
10. C-Cl Stretching Vibration -751.73 cm^{-1}, 695.19 cm^{-1}
11. Carboxylic acid Stretching Vibration- 2839.89 cm^{-1}
12. OH bending vibration for COOH - 963.11 cm^{-1}
13. C-F Stretching Vibration - 1111.98 cm^{-1}

B_1S

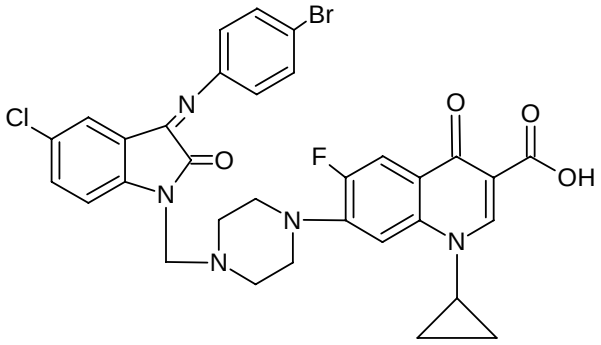


1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1760.11 cm^{-1}
3. C=N Stretching Vibration - 1738.62 cm^{-1}
4. C=C Aryl stretching Vibration - 1605.79 cm^{-1}
5. =NH imino Stretching Vibration - 3399.98 cm^{-1}
6. Para substitution in benzene ring - 832.79 cm^{-1}
7. Methylene bridge - 2922.45 cm^{-1}
8. Cyclo propane Stretching Vibration - 3064.91 cm^{-1}
9. C-F Stretching Vibration - 1001.11 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2516.98 cm^{-1}
11. OH bending vibration for COOH - 955.43 cm^{-1}

B_2S

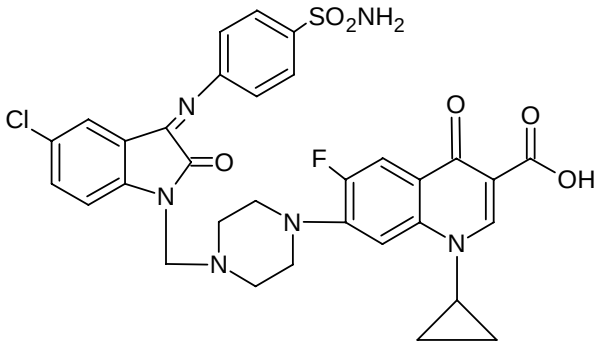


1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5'chloro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1720.64 cm^{-1}
3. C=N Stretching Vibration - 1621.09 cm^{-1}
4. C=C Aryl Stretching Vibration - 1580.80 cm^{-1}
5. =NH imino Stretching Vibration - 3398.76 cm^{-1}
6. C-Br Stretching Vibration -549.62 cm^{-1}
7. Para substitution in benzene ring - 823.46 cm^{-1}
8. Methylene bridge - 2927.19 cm^{-1}
9. Cyclo propane Stretching Vibration - 3127.49 cm^{-1}
10. C-Cl Stretching Vibration -746.18 cm^{-1}, 668.18 cm^{-1}
11. Carboxylic acid Stretching Vibration- 2837.99 cm^{-1}
12. OH bending vibration for COOH - 951.31 cm^{-1}
13. C-F Stretching Vibration - 1084.86 cm^{-1}

B_3S

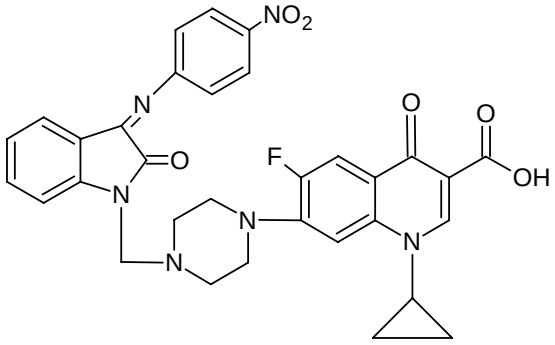


1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5' chloro-3'-[(4'-Sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1748.23 cm^{-1}
3. C=N Stretching Vibration - 1680.34 cm^{-1}
4. C=C Aryl stretching Vibration - 1615.09 cm^{-1}
5. NH Asymmetric Stretching Vibration - 3387.45 cm^{-1}
6. Para substitution in benzene ring - 835.26 cm^{-1}
7. Methylene bridge - 2924.31 cm^{-1}
8. Cyclo propane Stretching Vibration - 3039.71 cm^{-1}
9. C-F Stretching Vibration - 1091.96 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2749.12 cm^{-1}
11. S-N Stretching Vibration - 900.11cm^{-1}
12. SO_2 Asymmetric Stretching Vibration- 1330.45 cm^{-1}
13. SO_2 Symmetric Stretching Vibration - 1151.29 cm^{-1}
14. C-Cl Stretching Vibration - 736.45 cm^{-1}

CS

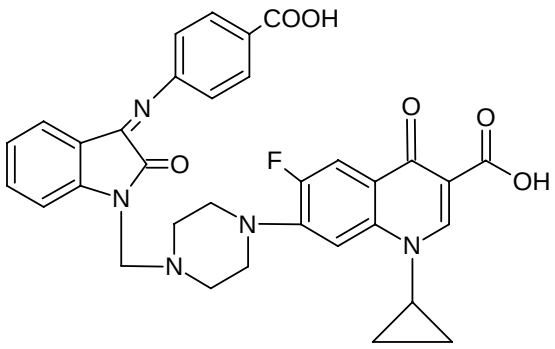


1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[3'-[(4'-nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1737.25 cm^{-1}
3. C=N Stretching Vibration - 1678.98 cm^{-1}
4. C=C Aryl Stretching Vibration - 1596.90 cm^{-1}
5. =NH imino Stretching Vibration - 3370.28 cm^{-1}
6. Aromatic nitro group - 1351.35 cm^{-1}
7. Para substitution in benzene ring - 831.70 cm^{-1}
8. Methylene bridge - 2925.61 cm^{-1}
9. Cyclo propane Stretching Vibration - 3103.80 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2855.52 cm^{-1}
11. OH bending vibration for COOH - 945.39 cm^{-1}
12. C-F Stretching Vibration - 1110.28 cm^{-1}

C_1S

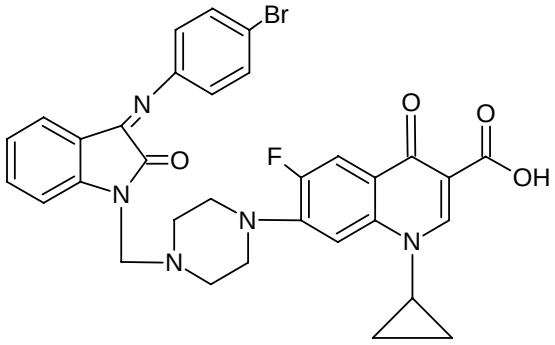


1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1736.64 cm^{-1}
3. C=N Stretching Vibration - 1678.82 cm^{-1}
4. C=C Aryl stretching Vibration - 1607.98 cm^{-1}
5. =NH imino Stretching Vibration - 3423.89 cm^{-1}
6. Para substitution in benzene ring - 833.94 cm^{-1}
7. Methylene bridge - 2927.71 cm^{-1}
8. Cyclo propane Stretching Vibration - 3090.86 cm^{-1}
9. C-F Stretching Vibration - 1065.20 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2843.56 cm^{-1}
11. OH bending vibration for COOH - 966.32 cm^{-1}

C_2S

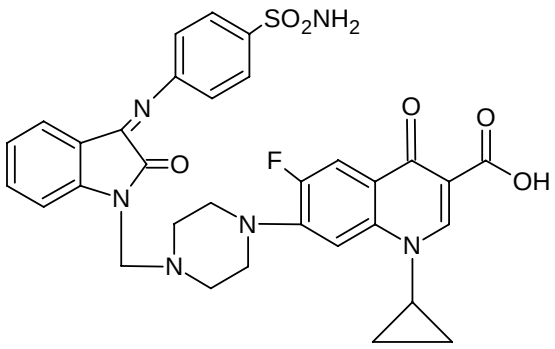


1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1711.48 cm^{-1}
3. C=N Stretching Vibration - 1690.12 cm^{-1}
4. C=C Aryl stretching Vibration - 1614.65 cm^{-1}
5. =NH imino Stretching Vibration - 3385.92 cm^{-1}
6. Para substitution in benzene ring - 847.21 cm^{-1}
7. Methylene bridge - 2924.23 cm^{-1}
8. Cyclo propane Stretching Vibration - 3052.91 cm^{-1}
9. C-F Stretching Vibration - 1108.34 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2698.74 cm^{-1}
11. OH bending vibration for COOH - 955.31 cm^{-1}

C_3S



1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[3'-[(4'-Sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

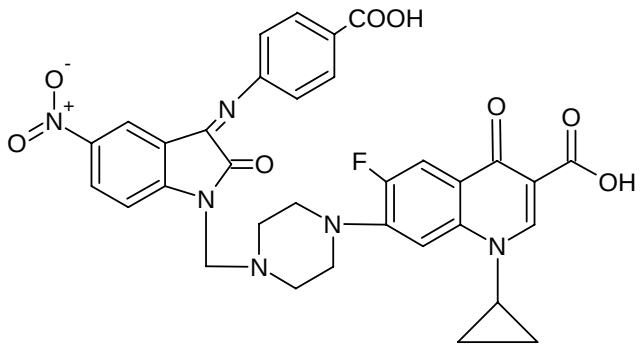
IR Values:

1. Aromatic Compounds - Above 3300 cm^{-1}
2. C=O Stretching Vibration - 1739.04 cm^{-1}
3. C=N Stretching Vibration - 1666.74 cm^{-1}
4. C=C Aryl stretching Vibration - 1611.46 cm^{-1}
5. NH Asymmetric Stretching Vibration - 3383.34 cm^{-1}
6. Para substitution in benzene ring - 830.83 cm^{-1}
7. Methylene bridge - 2925.80 cm^{-1}
8. Cyclo propane Stretching Vibration - 3100.31 cm^{-1}
9. C-F Stretching Vibration - 1095.05 cm^{-1}
10. Carboxylic acid Stretching Vibration- 2831.12 cm^{-1}
11. S-N Stretching Vibration - 900.97 cm^{-1}
12. SO_2 Asymmetric Stretching Vibration- 1334.25 cm^{-1}
13. SO_2 Symmetric Stretching Vibration - 1153.37 cm^{-1}

NUCLEAR MAGNETIC RESONANCE SPECTRAL ANALYSIS [66, 69, 70]

The structures of the synthesized compounds were elucidated by BRUCKER 300 MHz FT- NMR using TMS (Tetramethyl Silane) as internal standard. The Proton Magnetic Resonance Spectroscopic values are measured in δ ppm in $CDCl_3$.

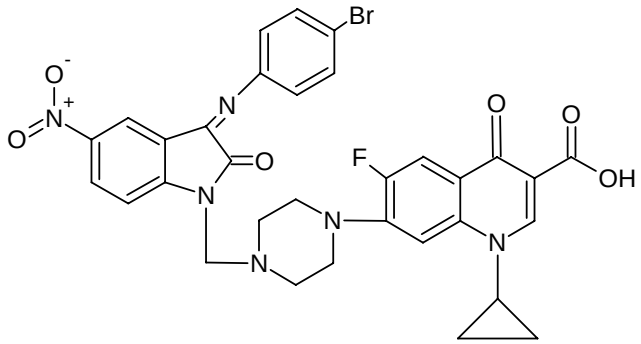
Sample A1S



1 -cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-carboxy phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

1.3	-	t, 2H,	Cyclopropane
1.6	-	s, 2H,	CH_2
3.123	-	m, 8H,	in Piperazine
7.972	-	m, 4H,	Indole
7.218-7.645	-	m, 6H,	Aromatic protons
11.4	-	s, H,	COOH

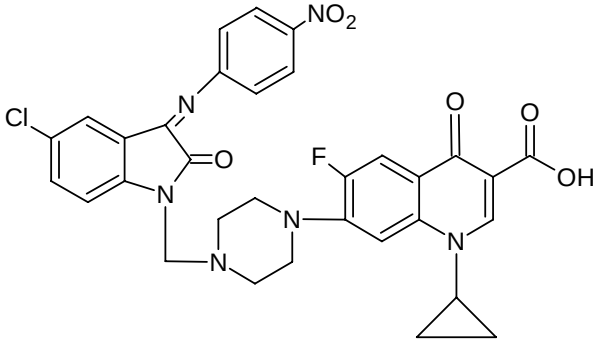
Sample A2S



1 -cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[N^4-[5'nitro-3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

1.4	-	t, 2H,	Cyclopropane
1.6	-	s, 2H,	CH_2
3.011-3.148	-	m, 8H,	in Piperazine
8.178	-	m, 4H,	Indole
7.282-7.735	-	m, 6H,	Aromatic protons
11.5	-	s, H,	COOH

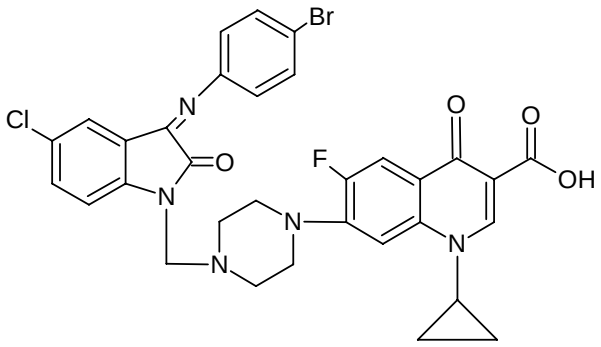
Sample BS



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5' chloro -3'-[(4'- nitro phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

1.3	-	t, 2H,	Cyclopropane
1.6	-	s, 2H,	CH_2
3.035-3.171	-	m, 8H,	in Piperazine
8.001	-	m, 4H,	Indole
7.047-7.784	-	m, 6H,	Aromatic protons
11.4	-	s, H,	COOH

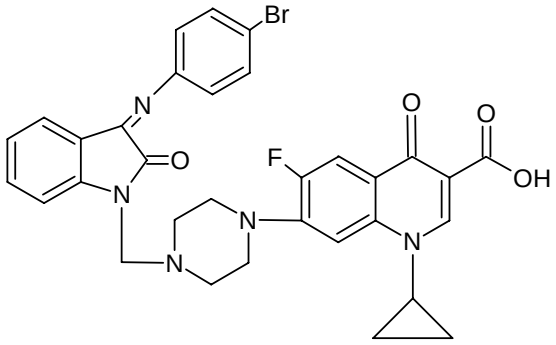
Sample B2S



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[5' chloro -3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid.

1.3	-	t, 2H,	Cyclopropane
1.6	-	s, 2H,	CH_2
3.009-3.101	-	m, 8H,	in Piperazine
7.964	-	m, 4H,	Indole
7.028-7.761	-	m, 6H,	Aromatic protons
11.5	-	s, H,	COOH

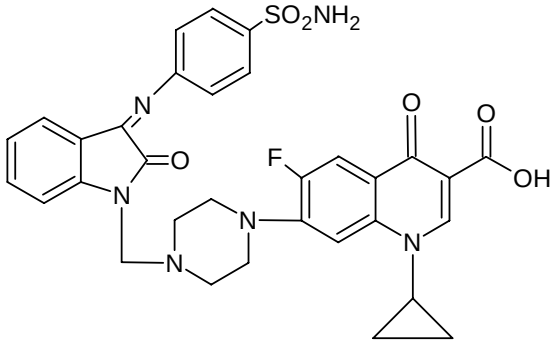
Sample C2S



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-bromo phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

1.3	-	t, 2H,	Cyclopropane
1.6	-	s, 2H,	CH_2
3.010-3.102	-	m, 8H,	in Piperazine
7.857	-	m, 4H,	Indole
7.037-7.646	-	m, 6H,	Aromatic protons
11.4	-	s, H,	COOH

Sample C3S



1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7[[N^4-[3'-[(4'-sulphamido phenyl)-imino-1'-isatinyl] methyl] N^1-piperazinyl]-3-quinoline carboxylic acid

1.3	-	t, 2H,	Cyclopropane
1.6	-	s, 2H,	CH_2
7.857	-	m, 4H,	Indole
7.037-7.646	-	m, 6H,	Aromatic protons
10.9	-	s, H,	COOH
9.8	-	s, 2H,	SO_2NH_2

ANTI-MICROBIAL SCREENING [24, 53, 73, 74]

Anti-bacterial and Anti-fungal activity [Cup and Plate method]

PROCEDURE:

Preparation of Muller – Hinton Agar

Beef extract	-	300 gm
Peptone	-	17.5 gm
Starch	-	1.5 gm
Agar	-	17 gm
Cold distilled water	-	up to 1000 ml.

Method:

All the ingredients were weighed and suspended in 1000 ml of cold distilled water and heated to boiling. The pH of the media was adjusted to 7.4 with 5 M sodium hydroxide solution. Then 5 – 20 ml of this agar medium was transferred into each boiling tube and plugged with non- absorbent cotton.

The tube containing agar medium was sterilized by pressure controlled heat sterilizations technique using an autoclave at 15 lbs at 121^{o}C for 20 minutes.

After sterilization the agar medium was melted, cooled and inoculated with G (+ ve) organisms like *Staphylococcus aureus, Streptococcus pyogenes,* G (- ve) organism *E .coli, Klebsilla aerogenes,* and *Candida albicans* (Fungi) then poured into sterile Petri dish to get a uniform thickness of 5 – 6 mm. Cups were made out in the other plate using sterile cork borer (6 dm).

Then the cups were charged with appropriate concentration of the standard like Ciprofloxacin (30µg/ml) and Ketoconazole (50µg/ml). Likewise the cups were also charged with the series of newly synthesized Isatin derivatives (30µg/ml) and incubated at 37^{o}C for 24 hours. The diameter of zone of inhibition around the cups were measured and tabulated in the following table

ANTI -BACTERIAL ACTIVITY OF TITLED COMPOUNDS

AGAINST G (+ ve) ORGANISMS

Table No: 4

S. No.	Compound Code	Zone of Inhibition (mm)	
		***Staphylococci* G(+ve)**	***Streptococci* G(+ve)**
1.	AS	18mm	17mm
2.	A1S	19mm	18mm
3.	A2S	16mm	14mm
4.	A3S	22mm	20mm
5.	BS	21mm	19mm
6.	B1S	22mm	20mm
7.	B2S	19mm	16mm
8.	B3S	23mm	21mm
9.	CS	10mm	8mm
10.	C1S	20mm	16mm
11.	C2S	20mm	21mm
12.	C3S	20mm	19mm
13.	Solvent Control	0mm	0mm
14.	Std Ciprofloxacin	16mm	18mm

ANTI -BACTERIAL ACTIVITY OF TITLED COMPOUNDS

AGAINST G (- ve) ORGANISMS

Table No:5

S. No.	Compound Code	Zone of Inhibition (mm)	
		E.coli ***G(-ve)***	***Klebsilla*** ***G(-ve)***
1.	AS	23mm	16mm
2.	A1S	23mm	17mm
3.	A2S	21mm	12mm
4.	A3S	24mm	18mm
5.	BS	28mm	10mm
6.	B1S	27mm	20mm
7.	B2S	28mm	14mm
8.	B3S	30mm	15mm
9.	CS	20mm	10mm
10.	C1S	25mm	12mm
11.	C2S	26mm	16mm
12.	C3S	30mm	13mm
13.	Solvent Control	0mm	0mm
14.	Std Ciprofloxacin	23mm	18mm

ANTI –FUNGAL ACTIVITY OF TITLED COMPOUNDS

Table No: 6

S. No.	Compound Code	Zone of Inhibition (mm)
		Candida albicans
1.	AS	10mm
2.	A1S	14mm
3.	A2S	12mm
4.	A3S	13mm
5.	BS	14mm
6.	B1S	12mm
7.	B2S	14mm
8.	B3S	13mm
9.	CS	10mm
10.	C1S	12mm
11.	C2S	13mm
12.	C3S	14mm
13.	Solvent Control	0mm
14.	Std Ketoconazole	18mm

ANALGESIC ACTIVITY [73, 75, 76]

Evaluation of analgesic activity

The analgesic activities of various synthesized compounds were screened by using acetic acid induced writhing test in mice. Mice of either sex weighing between 20 –25 gm were taken in14 groups of each 4 animals.

Diclofenac sodium 10mg/kg was used as a standard drug for comparison of analgesic activity. Writhing was induced by administration 0.2ml of 1%v/v of aceticacid through intraperitoneally. Record the number of abdominal contractions, trunk twist response and extension of hind limbs as well as the number of animals showing such response during a period of 25 min.

Administer all synthesized compound through I.P. Half an hour later administer aceticacid solution at 1ml/100gm B.W. Note and calculate onset and severity of writhing response. Note the inhibition of pain response by synthesized drugs.

EFFECT OF ANALGESIC ACTIVITIES OF SYNTHESIZED COMPOUNDS AGAINST ACETIC ACID INDUCED WRITHING TESTS IN MICE.

Table No: 7

GROUP	COMPD	DOSE	NO FO WRITHES IN 25MIN (Mean±.SEM)	%INHIBITION
G1(Normal control)	Normal saline	10 ml / kg	27.82±.0.42	-----
G2 (STD)	Diclofenac sodium	10 mg / kg	7.50±0.58.	73.04%
G3(Treatment control)	AS	5mg/ kg	8.60±0.43	69.08%*a
G4	A1S	5 mg/ kg	8.30±0.50	70.16%*a
G5	A2S	5 mg / kg	12.65±1.20	54.52%
G6	A3S	5 mg / kg	13.22±1.60	52.48%
G7	BS	5 mg / kg	8.90±0.71	68.00%*a
G8	B1S	5 mg / kg	13.05±1.12	53.09%
G9	B2S	5 mg / kg	8.58±0.70	69.15%*a
G10	B3S	5 mg / kg	12.60±1.20	54.70%
G11	CS	5 mg / kg	12.15±1.06	56.09%
G12	C1S	5 mg / kg	12.12±1.33	56.55%
G13	C2S	5 mg / kg	8.45±0.66	69.62%*a
G14	C3S	5 mg / kg	8.55±0.40	69.26%*a

- Values are expressed as Mean ± SEM
- Values are find out by using One way ANOVA followed by Newman Keul's multiple range tests.

*a Values are significantly different from normal control at P<0.01.

ULCEROGENIC ACTIVITY OF VARIOUS SYNTHESIZED ISATIN DERIVATIVES [74, 75, 76]

Acute Ulcerogenic test was carried out according to the Method of Cioli et al.[74] Wistar rats were divided into 14 Groups consisting of Six animals in each group.

Treatment Protocol as Follows:

Group I – Served as Normal Control (Received 0.5 ml of DMSO as Vehicle)

Group II – Served as Ulcer Control (Received Diclofenac Sodium 30mg/Kg).[75]

Group III to XIV – Served as Treatment Control (Received Synthetic Compounds such as AS, A1S, A2S, A3S, BS, B1S, B2S, B3S, CS, C1S, C2S, C3S at 5 mg/Kg respectively through I.P).

All animals were tested 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h[76] then they were Sacrificed.

The stomach was removed and opened along the Greater Curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosal damage examined by means of a Magnifying lens (10X).

For each stomach the mucosal damage was assessed according to the following scoring system.

Table No: 8

Score	Description
0.0	Normal (no injury, bleeding and latent injury)
0.5	Latent injury (or) Widespread bleeding (>2 mm)
1.0	Slight injury (2-3 dotted lines)
2.0	Severe injury (Continuous lined injury (or) 5-6 dotted injuries)
3.0	Very severe injury (Several Continuous lined injuries)

The Mean Score of each treated group minus Mean Score of control group was regarded as the Severity Index of Gastric Mucosal damage.

ULCEROGENIC EFFECTS OF SYNTHESIZED COMPOUNDS IN COMPARISON WITH DICLOFENAC SODIUM.

Table No: 9

Group	Dose (mg/Kg)	Ratio of ulcerated animals	Ulcer Index (Mean ± SEM)
I	0.5 ml DMSO	0/6	0.0 ± 0.0
II	30mg/Kg Diclofenac sodium	6/6	2.1 ± 0.2
III	5 mg/Kg AS	5/6	1.8 ± 0.3
IV	5 mg/Kg A1S	3/6	0.6 ± 0.1*a
V	5 mg/Kg A2S	2/6	0.5 ± 0.1*a
VI	5 mg/Kg A3S	4/6	1.9 ± 0.4
VII	5 mg/Kg BS	1/6	0.5 ±0.2 *a
VIII	5 mg/Kg B1S	5/6	2.0 ± 0.3
IX	5 mg/Kg B2S	1/6	0.8 ± 0.2*a
X	5 mg/Kg B3S	1/6	0.8 ± 0.2*a
XI	5 mg/Kg CS	5/6	1.5 ±0.5
XII	5 mg/Kg C1S	5/6	1.6 ± 0.3
XIII	5 mg/Kg C2S	2/6	0.6 ± 0.1*a
XIV	5 mg/Kg C3S	2/6	0.6 ± 0.1*a

Values are expressed as Mean ± SEM. Data analysed by one way ANOVA followed by Newman Kevi's Multiple range test.

[*a] – Values were significantly different from control at $p < 0.01$.

ANTI-MICROBIAL SCREENING [24, 53, 73, 74]

Anti-bacterial and Anti-fungal activity [Cup and Plate method]

PROCEDURE:

Preparation of Muller – Hinton Agar

Beef extract	-	300 gm
Peptone	-	17.5 gm
Starch	-	1.5 gm
Agar	-	17 gm
Cold distilled water	-	up to 1000 ml.

Method:

All the ingredients were weighed and suspended in 1000 ml of cold distilled water and heated to boiling. The pH of the media was adjusted to 7.4 with 5 M sodium hydroxide solution. Then 5 – 20 ml of this agar medium was transferred into each boiling tube and plugged with non- absorbent cotton.

The tube containing agar medium was sterilized by pressure controlled heat sterilizations technique using an autoclave at 15 lbs at 121^{o}C for 20 minutes.

After sterilization the agar medium was melted, cooled and inoculated with G (+ ve) organisms like *Staphylococcus aureus, Streptococcus pyogenes,* G (- ve) organism *E .coli, Klebsilla aerogenes,* and *Candida albicans* (Fungi) then poured into sterile Petri dish to get a uniform thickness of 5 – 6 mm. Cups were made out in the other plate using sterile cork borer (6 dm).

Then the cups were charged with appropriate concentration of the standard like Ciprofloxacin (30µg/ml) and Ketoconazole (50µg/ml). Likewise the cups were also charged with the series of newly synthesized Isatin derivatives (30µg/ml) and incubated at 37^{o}C for 24 hours. The diameter of zone of inhibition around the cups were measured and tabulated in the following table

ANTI -BACTERIAL ACTIVITY OF TITLED COMPOUNDS

AGAINST G (+ ve) ORGANISMS

Table No: 4

S. No.	Compound Code	Zone of Inhibition (mm)	
		***Staphylococci* G(+ve)**	***Streptococci* G(+ve)**
1.	AS	18mm	17mm
2.	A1S	19mm	18mm
3.	A2S	16mm	14mm
4.	A3S	22mm	20mm
5.	BS	21mm	19mm
6.	B1S	22mm	20mm
7.	B2S	19mm	16mm
8.	B3S	23mm	21mm
9.	CS	10mm	8mm
10.	C1S	20mm	16mm
11.	C2S	20mm	21mm
12.	C3S	20mm	19mm
13.	Solvent Control	0mm	0mm
14.	Std Ciprofloxacin	16mm	18mm

ANTI -BACTERIAL ACTIVITY OF TITLED COMPOUNDS

AGAINST G (- ve) ORGANISMS

Table No:5

S. No.	Compound Code	Zone of Inhibition (mm)	
		E.coli ***G(-ve)***	***Klebsilla*** ***G(-ve)***
1.	AS	23mm	16mm
2.	A1S	23mm	17mm
3.	A2S	21mm	12mm
4.	A3S	24mm	18mm
5.	BS	28mm	10mm
6.	B1S	27mm	20mm
7.	B2S	28mm	14mm
8.	B3S	30mm	15mm
9.	CS	20mm	10mm
10.	C1S	25mm	12mm
11.	C2S	26mm	16mm
12.	C3S	30mm	13mm
13.	Solvent Control	0mm	0mm
14.	Std Ciprofloxacin	23mm	18mm

ANTI –FUNGAL ACTIVITY OF TITLED COMPOUNDS

Table No: 6

S. No.	Compound Code	Zone of Inhibition (mm)
		Candida albicans
1.	AS	10mm
2.	A1S	14mm
3.	A2S	12mm
4.	A3S	13mm
5.	BS	14mm
6.	B1S	12mm
7.	B2S	14mm
8.	B3S	13mm
9.	CS	10mm
10.	C1S	12mm
11.	C2S	13mm
12.	C3S	14mm
13.	Solvent Control	0mm
14.	Std Ketoconazole	18mm

ANALGESIC ACTIVITY [73, 75, 76]

Evaluation of analgesic activity

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Diclofenac sodium 10mg/kg was used as a standard drug for comparison of analgesic activity. Writhing was induced by administration 0.2ml of 1%v/v of aceticacid through intraperitoneally. Record the number of abdominal contractions, trunk twist response and extension of hind limbs as well as the number of animals showing such response during a period of 25 min.

Administer all synthesized compound through I.P. Half an hour later administer aceticacid solution at 1ml/100gm B.W. Note and calculate onset and severity of writhing response. Note the inhibition of pain response by synthesized drugs.

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Table No: 7

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G2 (STD)	Diclofenac sodium	10 mg / kg	7.50±0.58.	73.04%
G3(Treatment control)	AS	5mg/ kg	8.60±0.43	69.08%*a
G4	A1S	5 mg/ kg	8.30±0.50	70.16%*a
G5	A2S	5 mg / kg	12.65±1.20	54.52%
G6	A3S	5 mg / kg	13.22±1.60	52.48%
G7	BS	5 mg / kg	8.90±0.71	68.00%*a
G8	B1S	5 mg / kg	13.05±1.12	53.09%
G9	B2S	5 mg / kg	8.58±0.70	69.15%*a
G10	B3S	5 mg / kg	12.60±1.20	54.70%
G11	CS	5 mg / kg	12.15±1.06	56.09%
G12	C1S	5 mg / kg	12.12±1.33	56.55%
G13	C2S	5 mg / kg	8.45±0.66	69.62%*a
G14	C3S	5 mg / kg	8.55±0.40	69.26%*a

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All animals were tested 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h[76] then they were Sacrificed.

The stomach was removed and opened along the Greater Curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosal damage examined by means of a Magnifying lens (10X).

For each stomach the mucosal damage was assessed according to the following scoring system.

Table No: 8

Score	Description
0.0	Normal (no injury, bleeding and latent injury)
0.5	Latent injury (or) Widespread bleeding (>2 mm)
1.0	Slight injury (2-3 dotted lines)
2.0	Severe injury (Continuous lined injury (or) 5-6 dotted injuries)
3.0	Very severe injury (Several Continuous lined injuries)

The Mean Score of each treated group minus Mean Score of control group was regarded as the Severity Index of Gastric Mucosal damage.

ULCEROGENIC EFFECTS OF SYNTHESIZED COMPOUNDS IN COMPARISON WITH DICLOFENAC SODIUM.

Table No: 9

Group	Dose (mg/Kg)	Ratio of ulcerated animals	Ulcer Index (Mean ± SEM)
I	0.5 ml DMSO	0/6	0.0 ± 0.0
II	30mg/Kg Diclofenac sodium	6/6	2.1 ± 0.2
III	5 mg/Kg AS	5/6	1.8 ± 0.3
IV	5 mg/Kg A1S	3/6	0.6 ± 0.1*a
V	5 mg/Kg A2S	2/6	0.5 ± 0.1*a
VI	5 mg/Kg A3S	4/6	1.9 ± 0.4
VII	5 mg/Kg BS	1/6	0.5 ±0.2 *a
VIII	5 mg/Kg B1S	5/6	2.0 ± 0.3
IX	5 mg/Kg B2S	1/6	0.8 ± 0.2*a
X	5 mg/Kg B3S	1/6	0.8 ± 0.2*a
XI	5 mg/Kg CS	5/6	1.5 ±0.5
XII	5 mg/Kg C1S	5/6	1.6 ± 0.3
XIII	5 mg/Kg C2S	2/6	0.6 ± 0.1*a
XIV	5 mg/Kg C3S	2/6	0.6 ± 0.1*a

Values are expressed as Mean ± SEM. Data analysed by one way ANOVA followed by Newman Kevi's Multiple range test.

[*a] – Values were significantly different from control at $p < 0.01$.

RESULTS AND DISCUSSION

SYNTHETIC METHODOLOGY:

The titled compounds were synthesized in a 2 step process:

- The first step in which Schiff's bases of Isatin derivatives were prepared by the treatment of **5-nitro Isatin, 5- Chloro Isatin, Isatin** with **p-Nitro aniline, PABA, p-bromo aniline and Sulphanilamide**

- The Second step was the Mannich Reaction. The presence of active hydrogen in **N-1 position** of Isatin facilitates the **Mannich reaction**. Mannich Bases were prepared by treating the Schiff's Bases of isatin derivatives with **Ciprofloxacin** in the presence of Formaldehyde.

Characterization:

- The **melting points** were found in an open end capillary tube method by electrically heating melting point apparatus and are uncorrected.
- The purity of the compounds were analysed by **Thin Layer chromatography** using Silica Gel (0.5 mm thickness) as stationary phase, employing Chloroform:Methanol (9:1) as Mobile phase, spots were visualized using Iodine vapours.

  The Rf value of the synthesized compounds were calculated.
- The characterization of the titled compounds including **Infrared and Nuclear Magnetic Resonance Spectral data** were in correlation with the expected structure.

PHARMACOLOGICAL SCREENING:

Anti Microbial Screening:

- Anti Microbial activity of the synthesized compounds were evaluated by **Cup and Plate method** against ***Staphylococcus aureus, Streptococcus pyogenes, Klebsilla aerogenes, Escherichia coli*** **and** ***Candida albicans***.

Anti Bacterial Screening:

- All the Synthesized Compounds Shows significant antibacterial activity against all the four Microorganisms when Compared to the Standard drug Ciprofloxacin.

- The Maximum degree of activity was observed against ***Staphylococcus aureus*** **and** ***Streptococcus pyogenes*** for compounds **AS, A1S, A2S, A3S, BS, B1S, B2S, B3S, C1S, C2S, C3S.** The compound CS shows moderate degree of activity when compared to standard drug Ciprofloxacin.

- All the Compounds exhibited greater activity against ***Escherichia coli*** when compared to standard drug Ciprofloxacin.

- Moderate Antibacterial activity was observed against ***Klebsilla aerogenes*** for all the synthesized compounds.

Anti Fungal Screening:

- All the titled compounds showed Moderate activity against the fungi ***Candida albicans.***

Analgesic Activity:

- The synthesized compounds were evaluated for Analgesic Activity by **Acetic acid Induced Writhing Method.**
- Compounds **AS, A1S, BS, B2S, C2S, and C3S** (5mg/kg)posses significant Analgesic activity**.** The writhing effect was significantly inhibited by the above compounds.
- The standard drug **Diclofenac Sodium** at a dose of 10mg/kg inhibited the writhing effect to a greater extent.
- Compounds like **A2S, A3S, B1S, B3S, CS and C1S**(5mg/kg) possess moderate analgesic activity when compared to standard group.

Ulcerogenic Index

- The **Maximum reduction in Ulcerogenic Index** (Mean Severity Index ± SEM, n=6) was **0.5 ± 0.1 to 0.8 ± 0.2,** found in synthesized compounds like **A1S, A2S, BS, B2S, B3S, C2S, C3S**.
- The other synthesized Compounds like **AS, A3S, B1S, CS, C1S,** Showed high severity of **Ulcerogenic Index** between1.5 to 2.0 equal to the Ulcerogenic index of the standard Diclofenac sodium (30mg/Kg) in Group II treated animals.

CONCLUSION

- ✓ **Novel Schiff's and Mannich Bases of Isatin Derivatives** were synthesized by a 2 step process.

- ✓ The **Melting points** were found for the synthesized compounds and are uncorrected. The purity of the synthesized compounds were analysed by **Thin Layer Chromatography methods.**

- ✓ The structures of the synthesized compounds has been elucidated by **Infrared and Nuclear Magnetic Resonance Spectroscopy.**

- ✓ The **Anti Microbial activity** of the synthesized compounds were screened by **Cup and Plate Method** against ***Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Klebsilla aerogenes*** and the fungi ***Candida albicans.***

- ✓ All the Compounds Showed **maximum activity** against ***Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli,*** and showed **Considerable activity** against ***Klebsilla aerogenes*** and the fungi ***Candida albicans***.

- ✓ Based on the results, it become evident that the attachment of various groups like **p-Nitro aniline, PABA, p-Bromo aniline and Sulphanilamide** to **isatin nucleus** along with **Ciprofloxacin exhibit greater anti bacterial activity** when **compared** to standard drug **Ciprofloxacin.**

- ✓ The **analgesic activity** of the synthesized compounds (5mg/kg) were screened by **Acetic Acid Induced Writhing metho**d in Albino rats against the standard drug Diclofenac sodium(25mg/kg)

- ✓ From the obtained results **the compounds AS, A1S, BS, B2S, C2S, and C3S** posses significant Analgesic activity**.**
- ✓ The **Ulcerogenic Index** of the synthesized compounds was evaluated according to the method of **Cioli et al**.
- ✓ The **Maximum reduction in Ulcerogenic Index** (Mean Severity Index ± SEM, n=6) was **0.5 ± 0.1 to 0.8 ± 0.2,** found in synthesized compounds like **A1S, A2S, BS, B2S, B3S, C2S, C3S**.
- ✓ Though this coverage is not exhaustive, the extended studies on various activities such as Anti Convulsant, Anti tumour, Anti Viral etc., and further pharmacological characterization of these compounds for host specific actions, toxic side effects and drug interactions are needed. Subsequent characterization on these aspects could bring these derivatives as successful therapeutic agent.

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